

## Review

## Touchscreen cognitive testing: Cross-species translation and co-clinical trials in neurodegenerative and neuropsychiatric disease

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## ARTICLE INFO

## Keywords:

Touchscreen cognition

Co-clinical trials

Neurodegenerative disease

Translational neuroscience

## ABSTRACT

Translating results from pre-clinical animal studies to successful human clinical trials in neurodegenerative and neuropsychiatric disease presents a significant challenge. While this issue is clearly multifaceted, the lack of reproducibility and poor translational validity of many paradigms used to assess cognition in animal models are central contributors to this challenge.

Computer-automated cognitive test batteries have the potential to substantially improve translation between pre-clinical studies and clinical trials by increasing both reproducibility and translational validity. Given the structured nature of data output, computer-automated tests also lend themselves to increased data sharing and other open science good practices. Over the past two decades, computer automated, touchscreen-based cognitive testing methods have been developed for non-human primate and rodent models. These automated methods lend themselves to increased standardization, hence reproducibility, and have become increasingly important for the elucidation of the neurobiological basis of cognition in animal models. More recently, there have been increased efforts to use these methods to enhance translational validity by developing task batteries that are nearly identical across different species via forward (i.e., translating animal tasks to humans) and reverse (i.e., translating human tasks to animals) translation.

An additional benefit of the touchscreen approach is that a cross-species cognitive test battery makes it possible to implement co-clinical trials—an approach developed initially in cancer research—for novel treatments for neurodegenerative disorders. Co-clinical trials bring together pre-clinical and early clinical studies, which facilitates testing of novel treatments in mouse models with underlying genetic or other changes, and can help to stratify patients on the basis of genetic, molecular, or cognitive criteria. This approach can help to determine which patients should be enrolled in specific clinical trials and can facilitate repositioning and/or repurposing of previously approved drugs. This has the potential to mitigate the resources required to study treatment responses in large numbers of human patients.

### 1. Introduction

Neurodegenerative and neuropsychiatric diseases contribute to

diminished quality of life for millions of patients and their caregivers. These conditions include Alzheimer's disease, fronto-temporal dementia, schizophrenia, Huntington's disease, and Parkinson's disease. These

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<https://doi.org/10.1016/j.nlm.2021.107443>

Received 5 September 2020; Received in revised form 6 February 2021; Accepted 26 February 2021

Available online 22 April 2021

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disorders have a tremendous impact on cognition—affecting aspects such as memory, attention, and cognitive flexibility—and are also characterized by mental health symptoms such as depression, anxiety and impulsivity. In addition to being devastating to the individual, neurodegenerative and neuropsychiatric diseases are a major public health challenge. It has been estimated that cost of neurodegenerative diseases alone can be as high as £134 billion in the UK (Fineberg et al., 2013) and as high as \$800 billion in the United States (Gooch et al., 2017). Although several approved treatments for neurodegenerative diseases exist, none at the moment seem to be mechanistically linked to disease modification.

There is clearly a pressing need for new treatments for neurodegenerative and neuropsychiatric disorders (Huang & Mucke, 2012; Liu et al., 2019; Mehta et al., 2017; Oxford et al., 2020). So far, however, the substantial advances made in understanding the fundamental neurobiology of the brain have not translated to success in the clinic, and over the past 3 decades, novel treatments for these disorders have been few (Anand & Singh, 2013; Kaduszkiewicz et al., 2005; Raina et al., 2008). This lack of progress is not due to an absence of ongoing efforts, as many new clinical trials have been conducted in recent years (Lang & Espay, 2018; Petrov et al., 2017; Tsai & Boxer, 2016), but rather to the failure of new brain disease-targeting drugs to have significant clinical impact relative to most other areas of drug discovery (Mehta et al., 2017; Olanow et al., 2008). Worryingly, many pharmaceutical companies have therefore now closed their neuroscience divisions to focus on what they consider to be more treatable conditions (BBC, 2018; Fleming, 2018; Skripka-Serry, 2013).

What underlies this high failure rate? One issue is that decisions to progress drugs into clinical trials are heavily based on pre-clinical work in animal models. Animal models are essential as they allow investigation of the brain using methods that would not be possible in humans. If a mouse model displays underlying biology associated with human disease (e.g., a specific genetic mutation or pathology), along with functional outcomes that mimic the human disease (e.g., cognitive dysfunction), such a model can be useful to help predict whether a drug will work in humans. However, potential treatments for brain conditions repeatedly fail in humans despite seemingly adequate and appropriate data in animal models demonstrating that candidate drugs should work (Mehta et al., 2017; Olanow et al., 2008).

Thus there is a growing awareness that building better bridges across the gap between pre-clinical animal models and research in humans is critical to the development of new treatments (Anderzhanova et al., 2017; Hvoslef-Eide et al., 2016; Stoyanov, 2017). Three outstanding issues are currently at the forefront of this discussion: 1) How effectively pre-clinical studies are conducted, including issues around sample size (Button et al., 2013), selection bias (Beery & Zucker, 2011; Gottlieb & Oudeyer, 2018), and unidentified confounding variables such as experimenter and other environmental factors (Green, 2015). 2) The relevance to humans of the functional outcomes—including cognition and behavior—that are assessed in animal models (i.e., translational validity of cognitive behavioral testing; Hånell & Marklund, 2014). 3) How effectively rodent models recapitulate human disease and its progression. This review focusses on how a touchscreen-based cognitive testing platform for animal models and humans addresses the first two of these issues; discussions of how well models recapitulate human disease can be found elsewhere (Chadman et al., 2009; Markou et al., 2009; Onos et al., 2019; Stewart & Kalueff, 2015).

## 2. Gaps in translation from pre-clinical animal models to humans

### 2.1. Reproducibility in neuroscience: How effectively are pre-clinical studies conducted?

One of the major issues hampering animal disease model research is the lack of methodological consistency, which can impact

reproducibility (Hantula, 2019; Jilka, 2016; Jonker et al., 2013; Macleod & Mohan, 2019). While many studies identifying issues with replication have focused on human psychology, there have been several key studies that have identified methodological and other issues that may affect reproducibility in animal studies across a variety of fields (Arseneau & Cominelli, 2017; Crabbe et al., 1999; Crook et al., 2020; Gerlai, 2019; Hentze & Ibsen, 2019; McDougal et al., 2016; Ramirez et al., 2017; Turner, 2018). These issues can bring into question the validity of the results on which clinical trials are based. Therefore, any methodology that attempts to reduce the translational gap will need to consider how to increase the accuracy and rigor with which we conduct animal studies to improve reproducibility.

One way to improve reproducibility, and by extension enhance the probability of clinical translation, is by increasing standardization. Unlike in other fields, standardization of behavioral testing is rare. For example, a recent literature review revealed that many of the animal studies testing mouse models relevant to Alzheimer's Disease (AD) in the Morris Water Maze used significantly different apparatus sizes, pool temperatures, training session lengths, and training protocols, thus complicating the interpretation of the results (Egan et al., 2016). In contrast, standardized behavioral paradigms can help to ensure that findings compare across studies and sites, thus facilitating interpretation. Standardization of well-validated methodology can directly improve the replicability of an experiment, which will provide greater confidence in moving forward to a clinical trial.

### 2.2. Translational validity in neuroscience: How relevant to humans are the functional outcomes—including cognition and behavior—that are assessed in animal models?

Many standard tasks used to assess cognition in animal models have been designed to measure cognitive constructs similar to human cognitive constructs, including tests of learning, memory, behavioral flexibility, etc. There remains a degree of uncertainty, however, about whether a given test recruits the same cognitive processes in animals and humans, especially when animal and human tests can differ profoundly in their levels of stress (e.g., due to perceived danger), responses (e.g., large-environment navigation), and task motivation (e.g., escape from electrical shock). Clearly, if the constructs that are being measured in animal tasks do not represent the constructs tested in human tasks, then animal-human translation will be very difficult to achieve (Deslauriers et al., 2018; Driscoll & Barr, 2016; Flores et al., 2018; Insel, 2010; Malkesman et al., 2009; Wallace et al., 2015).

Importantly, this consideration extends to the primary sensory modality animals use to guide their behavior. While humans and non-human primates (NHPs) primarily guide behavior using vision, rodents possess low visual acuity that is hampered by small and laterally located eyes that poorly focus light (Artal et al., 1998; Burn, 2008; Huberman & Niell, 2011; Prusky & Douglas, 2004), and so tend to use olfactory and non-visual sensory information, including tactile information (collected from whiskers), more than humans. Nevertheless, while vision may not provide rodents with the most sensitive sensory information, the mouse and human visual system share enough similarities that mice are increasingly being used as a model for understanding human vision (Huberman & Niell, 2011; Krebs et al., 2017; Prusky & Douglas, 2004; Storchi et al., 2019; Zoccolan et al., 2009). Furthermore, the use of visual stimuli, which are easy to control, avoids some disadvantages of methods using other modalities (for example the difficulty of controlling odor presentation, particularly in tasks in which the animal interacts with (e.g., digs in) the stimulus). Finally, for the particular goal of animal-to-human cognitive translation, the fact that human participants are most often tested in the visual modality provides a strong impetus to develop well-validated tests for animals in the visual modality. It is now well established that rodents are adept at using complex visual cues in cognitive tests (Bartko et al., 2007; Bussey et al., 2002; Crijns & Op de Beeck, 2020; Kim, Hvoslef-Eide, et al., 2015; Lester

et al., 2020; Talpos et al., 2009; Wang & Krauzlis, 2018; Youngstrom & Strowbridge, 2012).

To achieve cross-species behavioural translation, two primary approaches can be taken: 1) forward translation, the modification of animal cognitive tasks for human testing, and 2) reverse translation (sometimes called back- or backward translation), the modification of human cognitive tasks for animal testing.

### 2.3. Forward translation

Several maze-based tasks have been translated from animals to humans by creating virtual environments in which participants can “navigate” (usually virtually) to find rewards, akin to the rodent radial arm maze, or find a hidden location as in the Morris Water Maze (Bohbot et al., 2004; 2007; 2017; Bohbot & Corkin, 2007; Cornwell et al., 2008; Ferguson et al., 2019; Iaria et al., 2003; Maguire et al., 2006; Skelton et al., 2006; van Gerven et al., 2016). Typically, participants use a mouse, keyboard or joystick to navigate; thus these approaches are compatible with neuroimaging which requires participants to keep their heads still for accurate readings (Antonova et al., 2011; Folley et al., 2010; Rodriguez, 2010). Virtual environments may, however, potentially recruit different neural systems compared to freely moving conditions (Taube et al., 2013). It is important to note that these limitations are greatly reduced with newer virtual reality paradigms, which can be immersive, requiring participants to make whole body movements in space (Chan et al., 2019; Park et al., 2011). However, these are often incompatible with neuroimaging due to free movement (Salgado-Pineda et al., 2004; Serino et al., 2015; Spieker et al., 2012). Moreover, many navigation tests in rodents are motivated by aversive stimuli, and it is not normally desirable to reproduce the stressful elements of animal tests in human tests (Iivonen et al., 2003; Janickova et al., 2019). Another approach to translating rodent tasks to humans has been to test humans’ ability to navigate large maze-like apparatuses that exist in the real-world environment (Bohbot et al., 2017; Laczó et al., 2010; Menenga et al., 2014). For example, famous neuropsychological patient HM was tested in a dry version of the water maze task known as the Invisible Sensor Test (Bohbot & Corkin, 2007).

### 2.4. Reverse translation

An approach to reverse translation to convert human cognitive tasks to animal tasks, in way that avoids the navigational demands and stressors present in maze tasks, is the use of operant chambers. Operant chambers, fitted with either levers or nose-poke holes in which approaches can be detected via infra-red beams, are automated and computer-controlled, allowing for a higher throughput and improved control of the testing environment. For example, working memory has been tested using lever-based delayed match- or non-match to sample tasks (e.g left vs right, Auger et al., 2020; Auger & Floresco, 2017; Dunnett, 1985; Dunnett et al., 1989). This sample, delay, choice paradigm closely parallels the format of human and NHP working memory tests (Hunter, 1913; Mello, 1971; Mishkin, 1982). A second early example of reverse translation using operant chambers was the development of the 9-hole operant box by Trevor Robbins and colleagues (Carli et al., 1983; Robbins, 2002), which adapted an attention task used in humans (Leonard, 1959) to create the rodent 5-choice serial reaction time task (5-CSRTT). In the 5-CSRTT, participants respond to brief light flashes as they are continuously presented. The rodent version of the task closely matches the human protocol, requiring rodents to monitor a display in order to detect and respond to a briefly illuminated location to collect a food reward. The 5-CSRTT has become one of the most commonly used operant tasks to assess attentional processes in both rats and mice.

Rodent touchscreen testing chambers are essentially an extension of traditional operant systems. The incorporation of a touchscreen instead of levers or nose-poke ports increases the range of stimuli and types of

cognitive tests that can be presented. An additional advantage is that touchscreen-based testing is increasingly used to assess cognition in humans, and using similar apparatus in humans and animal models facilitates reverse translation (Fig. 1). Touchscreen testing has been successfully adapted to a variety of animal species including NHPs (Dias et al., 1996; Gaffan et al., 1989; Gaffan et al., 1984; Pearce et al., 1998; Roberts et al., 1994), birds (Iwasaki et al., 2018; Watanabe et al., 2019; Watanabe, 2010; Watanabe et al., 2011; Wilkie et al., 1994; Yamamoto et al., 2015), and rodents (Bussey et al., 1994; Bussey et al., 2002), and is currently being further adapted for porcine cognitive research (see recent unpublished work by [The Allen Neurocircuitry & Cognition Lab](http://allenlab.fiu.edu/a-pig-model-for-behavioral-neuroscience/), Florida International University), <http://allenlab.fiu.edu/a-pig-model-for-behavioral-neuroscience/>). By using touchscreen technology, animal models can engage in computerized cognitive tasks that can be identical to those used in human studies (Bussey et al., 2012; Hvoslef-Eide et al., 2015). Over 20 tests of this type are available in cognitive domains including cognitive flexibility, learning, memory, motivation, attention, and decision making within the rodent touchscreen system (see Table 1, Sullivan et al., 2020) In recent years, automated touchscreen tasks have been used to study cognition in a number of genetic rodent models of diseases including schizophrenia (Nilsson et al., 2016; 2018; Saito et al., 2020; Zeleznikow-Johnston et al., 2018), Parkinson’s Disease (PD; Kwak et al., 2016), Huntington’s Disease (HD; Farrar et al., 2014; Glynn et al., 2016; Heath et al., 2019; Piipponiemi et al., 2018), and Down Syndrome (DS; Siegel et al., 2020). Touchscreen test batteries have been particularly useful for characterizing cognitive impairment profiles in genetic models of AD (Beraldo et al., 2019; Romberg et al., 2011).

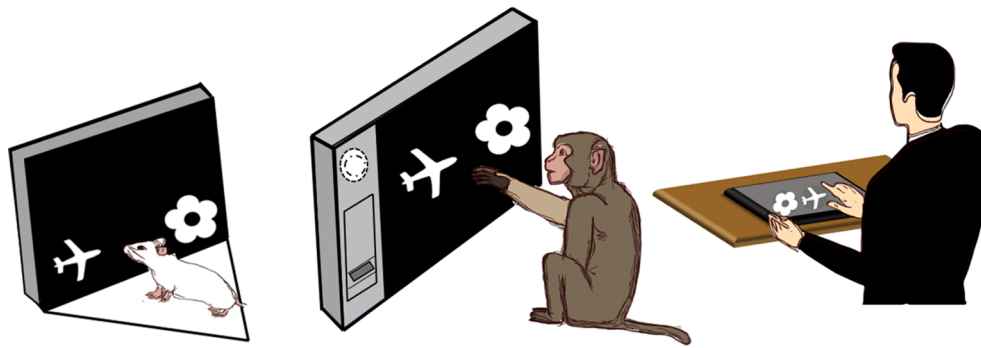
Rodent touchscreen technology lends itself to standardization: the same chambers, stimuli and task programs can be used across studies in any research facility around the world. Automated and standardized apparatus facilitates the creation of standardized operating procedures (SOPs) and best practices for rodent testing, as well as cross-facility comparisons of animal models (Beraldo et al., 2019). Furthermore, standardization allows for the growth of an epistemic research community by sharing these best practices, troubleshooting issues, and other resources (see for example [TouchscreenCognition.org](http://TouchscreenCognition.org)).

In addition to standardized behavioral protocols for cognitive testing, the rodent touchscreens also collect and output data in a standardized manner. This feature allows data to be compiled in a public data repository, where researchers can access, re-combine, and re-analyze the data, facilitating collaborative global efforts to understand the nervous system in health and disease (Beraldo et al., 2019). Indeed, online databases have been proposed as one possible solution to reducing the replication crisis by providing access to raw data (Miyakawa, 2020). Such a database for rodent touchscreen cognitive testing can be found at [MouseBytes.ca](http://MouseBytes.ca). Analysis of data from the first ~620 of the >1400 mice currently represented in [MouseBytes.ca](http://MouseBytes.ca) indicates a high degree of replicability of touchscreen data across laboratories (Beraldo et al., 2019).

While standardization of behavioral protocols is a powerful approach to addressing the potential inconsistency of findings, it is important to note that intentional variations in methodology are an important component of the initial development of tasks (Kim, Heath, et al., 2015; Oomen et al., 2015; Talpos et al., 2009). Controlled and intentional variations in techniques and testing practices aid in isolating behavioral nuances and can facilitate the development of behavioral tasks to address specific questions. (For example the TUNL touchscreen test of working memory and pattern separation was simplified to create a task – Location discrimination(LD) – geared toward research into pattern separation solely and specifically (McTighe et al., 2009)).

Once a test is developed, it must be validated, to show that it taps the neural circuits and cognitive constructs it was designed to tap. No one would demand a poorly validated test should become the standard. Only when a task is well-validated is it ready for standardization.

This is not to say that tasks cannot undergo periodic improvements.



**Fig. 1.** Translational neuroscience potential for touchscreen technology. Touchscreen technology can be used in human participants with tablet-based tasks, as well as in operant systems for NHPs and rodents. Screens display the paired associative learning (PAL) task across species. Created by Hannah Bigelow, MA.

For example, different genetic models may require modified task SOPs to shorten training time or animals may need to be given additional trials for meaningful data to be gathered (Heath et al., 2016). For this reason, touchscreencognition.org welcomes (validated) SOPs for new tasks, variations on SOPs for different purposes, as well as crowdsourced feedback on existing SOPs, which are in a continuous state of optimization. Furthermore, the goal of standardization is to provide best practices and improve the quality of research. The ideal model, then, is one under which well-validated tests are standardized, at the same time allowing for variation when circumstances demand it. In the next section, we expand on this issue of test validity.

### 3. The development of touchscreen cognitive testing systems: From human to monkey to mouse

#### 3.1. Touchscreen technology in human cognitive testing

With the development of personal computers came a revolution in cognitive testing for psychologists and neuroscientists. These systems allowed cognitive tasks to become better automated and more complex, while providing more precise and reliable results. Typically, the majority of computerized cognitive tests in humans use a mouse, keyboard, or button pad to register responses. These mechanical response options have been popular due to their use of familiar and easily available technology. Furthermore, they require little to no additional setup. In the last few decades, the global development of tablets and smartphones has made touchscreen-based devices increasing familiar and accessible. For this and other reasons (see below), there has been a steep rise in the use of touchscreens for cognitive testing. Touchscreen technology allows participants to respond directly to stimuli on a screen using their finger, rather than using a mechanical response system. Responding directly to stimuli on the screen increases stimulus–response contiguity and reduces unwanted demands that divided attention by ensuring spatial consistency with stimulus and response (particularly relevant in studies of neurodegenerative disease; Jenkins et al., 2016; Tsoy et al., 2019).

One of the earliest attempts at developing touchscreen-based cognitive tasks resulted in the Cambridge Automated Neuropsychological Test Associated Battery (CANTAB). Towards the end of the 1980's, Trevor Robbins, Barbara Sahakian and their colleagues developed multiple cognitive tasks that could be completed using an infrared-sensor touchscreen system (Fray et al., 1996; Sahakian et al., 1988; Sahakian & Owen, 1992). Over time, the CANTAB test battery grew to include a large collection of tasks to assess numerous cognitive processes including attention, memory, cognitive flexibility, and emotional cognition. Many of the tasks have been validated over the years as having diagnostic validity for assessing patients with disorders such as schizophrenia (Levaux et al., 2007; Young et al., 2013), PD (Stefanova et al., 2006), Autism Spectrum Disorder (ASD; Chien et al., 2015; Jiang et al., 2014), Multiple Sclerosis (MS; Foong et al., 1997), and Traumatic

Brain Injury (TBI; Salmond et al., 2005; Sterr et al., 2006). For example, the Paired Associate Learning (PAL) task has been used to assess memory impairments in neurodegenerative diseases such as AD and PD (Blackwell et al., 2003; Fowler et al., 1995; Sahakian et al., 1988; Sahakian et al., 1993), neuropsychiatric disorders such as schizophrenia (Elliott et al., 1995; Kéri et al., 2012) as well as in patients with localized brain damage (Robbins et al., 1998). PAL has been proven multiple times to be effective at identifying probable Alzheimer's patients and that predictive capacity can be significantly higher when paired with verbal memory assessments (Blackwell et al., 2003). In addition to AD, CANTAB has been used extensively to profile the mild cognitive impairment associated with aging (Cabral Soares et al., 2014; Égerházi et al., 2007; Juncos-Rabadán et al., 2014; Robbins et al., 1994)

Other examples of touchscreen cognitive testing include the Cogstate battery, which has been validated across a few settings and has been shown to be useful in the cognitive testing of patients with Human Immunodeficiency Virus (HIV; Overton et al., 2011), AD (Maruff et al., 2013), and schizophrenia (Pietrzak et al., 2009; Yoshida et al., 2011). Cambridge Brain Sciences has developed the CBS touchscreen test batteries that have been used to assess patients with conditions such as Alzheimer's (Huntley et al., 2017), and concussion (Stafford et al., 2020). The Computer-Administered Neuropsychological Screen for Mild Cognitive Impairment (CANS-MCI) test battery is a series of touchscreen cognitive tasks that have been shown to be effective in screening patients with mild cognitive impairment (Memória et al., 2014; Tornatore et al., 2005). Researchers from the University of California San Francisco recently developed the TabCAT test battery system, which has been shown to identify patients likely to convert to AD within a group of patients initially diagnosed with MCI (Possin et al., 2018; Elena Tsoy et al., 2020). More recently, researchers from Taiwan developed a new tablet-based touchscreen cognitive battery that tests attention, visual memory, and information processing. This new tablet-based battery was found to discriminate between healthy controls, patients with mild cognitive impairment, and those with probable AD (Huang et al., 2019).

With the development of these new tablet-based touchscreen batteries, there have been several studies addressing the use of this technology in cognitive testing. For example, a recent study gave a wide range of participants a touchscreen-based cognitive task and asked them to provide qualitative feedback (Jenkins et al., 2016). Jenkins et al. (2016) found that participants liked the “gamified” elements of the tasks and found them engaging. However, the authors also highlighted some key issues of which researchers must be mindful, for example variability in how participants respond to the screen, and the effect of ergonomics (e. g., position, angle, etc.) on participants' perception of the task. Others have pointed out that despite some of these issues, touchscreen tasks can be potentially more powerful than standard computer tasks by taking advantage of the additional sensors featured on tablets and smartphones (Koo & Vizer, 2019). Overall, it is clear that touchscreen tablet based cognitive testing is emerging as an important tool for screening

cognition in patients, due to its significant advantages with portability, which allows for researchers to test participants more easily within the clinical setting.

### 3.2. Touchscreen technology in non-human primate cognitive testing

Prior to the introduction of screen-based cognitive tasks for NHPs, assessments were classically performed using apparatus such as the Wisconsin General Testing Apparatus (WGTA), which involves the use of objects placed over food wells to implement tasks designed to probe functions such as learning, memory or executive functioning (Harlow, 1949; Harlow & Bromer, 1938; Schrier, 1961). The use of touchscreen systems to test NHPs, introduced in the 1980s, used a television placed behind a bezel housing infra-red emitters and detectors to localize touch responses (Gaffan et al., 1984). The close temporal association between stimulus presentation and response outcome was an attractive feature of this apparatus, as subjects could make a single motor response (i.e. finger touch) to the screen and receive immediate feedback (i.e. reward or not), rather than the multi-step process of evaluating 3-dimensional objects, displacing them, and then retrieving a food reward (Gaffan & Harrison, 1987). The touchscreen apparatuses provided a valuable tool for studying the brain structures involved in visual learning by combining targeted lesions with tasks designed to isolate specific learning processes. This included early assessments of the inferotemporal cortex in visual discrimination (Gaffan et al., 1986), amygdala-cortex connections during reward associated learning (Gaffan et al., 1989; Gaffan & Harrison, 1987; Gaffan et al., 1988), and the fornix during visuomotor learning (Brasted et al., 2002; Gaffan et al., 1984; Gaffan et al., 1988; Rupniak & Gaffan, 1987). Additionally, computerized graphics provided researchers the opportunity to create large lists of novel stimuli (>400), which could be designed similarly to images used in human tasks and presented on the touchscreen. The value of stimulus optimization was demonstrated by Roberts and colleagues (1988), who presented identical stimuli to human subjects and marmosets to assess common strategies in visual discrimination learning and set-shifting across species. Further, Gaffan (1994) created hundreds of unique object-in-place scenes by having backgrounds randomly generated using algorithms to create stimuli such as ellipses and ASCII characters that varied in size, color and location. It was found that generating scenes in the presentation facilitated the learning of ASCII characters in monkeys (Gaffan, 1994). Each day of testing, novel lists could be used to examine scene learning, which was often achieved within a single trial. The rapid learning of scenes or “snapshots” is thought to underlie aspects of episodic memory in humans (Baxter et al., 2007; Browning et al., 2010; Gaffan, 1994; Mitchell et al., 2007; Parker & Gaffan, 1997).

Importantly, the touchscreen system offered an avenue for evaluating the conservation of common neural mechanisms underlying cognitive processes between humans and NHPs. These included various cognitive domains including intra-dimensional and extra-dimensional set-shifting (Dias et al., 1996; Pearce et al., 1998; Roberts et al., 1992, 1994), recency and novelty judgments (Charles et al., 2004) among others (e.g., spatial-visual discriminations, Buckley, Charles, Browning, & Gaffan, 2004). For example, transections of the fornix in both humans and rhesus macaques can lead to memory impairments (D’Esposito et al., 1995; Gaffan, 1994). These experiments were instrumental in providing strong evidence for homologous brain structures supporting these processes across humans and NHPs.

Together, initial touchscreen-based experiments highlighted the benefit of a controlled, visually-based testing apparatus for probing the neurobiological underpinnings of behavior while maintaining methodological consistency across paradigms. For example, Collins and colleagues (1998) performed an elegant series of experiments using a novel spatial self-ordered sequencing touchscreen task in marmosets. This study implemented multiple versions of the task designed to isolate individual processes within the context of self-ordered sequencing tasks, including working memory, inhibitory control, and response sequencing

ability. In doing this, the researchers demonstrated that while lesions of the prefrontal cortex impaired performance on general spatial self-orienting tasks, these impairments were due to disrupted inhibitory control and working memory, but not response sequencing. This design highlighted the ability of these tasks to distinguish behaviorally relevant task aspects, making it possible to dissociate the contributions of brain regions to specific cognitive processes (Collins et al., 1998).

The adaptation of a CANTAB battery for NHPs reflected an important step toward commercializing standardized task batteries for animal cognitive testing. The non-verbal nature of touchscreen-based tasks made them ideal for use in NHPs, and the task battery allowed for multi-task evaluations of NHPs similar to protocols used in human clinical settings (Weed et al., 1999). Early implementations of the monkey CANTAB battery included tests of short-term memory, spatial working memory, cognitive flexibility, motivation, reaction time, and attention (Spinelli et al., 2004; Taffe et al., 1999; Weed et al., 1999). These investigations provided evidence for similar task-solving strategies in NHPs and humans, for example by analysis of characteristic error profiles and performance reduction following increased task difficulty. Furthermore, these groups demonstrated that animals’ task performance could be maintained over extended periods of time, which suggested that these paradigms would be valuable for studying cognition in a longitudinal manner (Nagahara et al., 2010). The development of monkey CANTAB tasks included the adaptation of the visuo-spatial paired-associate learning (vsPAL) task relevant to the study of dementia and AD (Gould et al., 2005; Taffe et al., 2002; see above). Pharmacological studies using vsPAL revealed similar detrimental effects of N-methyl-D-aspartate (NMDA) antagonists, and beneficial effects of nicotine, on memory processes between humans and NHPs (Katner et al., 2004; Taffe et al., 2002; 2004), as well as impairments following dopamine receptor 2 (D<sub>2</sub>) antagonist administration in Rhesus monkeys (Von Huben et al., 2006). The CANTAB battery has also been used to assess cognitive decline in aged NHPs, which demonstrated deficits in visuospatial learning (vsPAL), spatial working memory (self-ordered spatial search task), and initial discrimination learning (Nagahara et al., 2010), akin to the impairment profile observed in aging humans (Mutter et al., 2006; Rabbitt & Lowe, 2000; Robbins et al., 1994; Robbins et al., 1998). With the continued use of NHPs to model cognition in normal and pathological conditions, administering automated test batteries using touchscreens has the potential to provide a standardized performance assessment for various NHP species that can be referenced for planning and interpreting succeeding studies (Kangas et al., 2016; Kangas & Bergman, 2014).

An important consideration for using touchscreen-based tasks with non-human animals is the requirement for continuous primary reward feedback during training, which is absent in human variants, and may recruit additional processes involved in reward learning (Barnett et al., 2016). Further, implementation of test batteries needs to consider the species of study. For example, despite comparable performance ability, macaques can be tested on multiple tasks during a single session, whereas more evolutionarily distinct monkeys such as marmosets may have to be trained and tested on individual tasks (Kangas & Bergman, 2017; Spinelli et al., 2004). Additionally, primates such as marmosets may possess either dichromatic or trichromatic vision depending on sex, leading to variation in color perception which may introduce variability or confounds if stimulus features are not carefully selected (Pessoa et al., 2005; Roberts et al., 1988; Travis et al., 1985). Taken together, the integration of touchscreen paradigms for NHPs has provided key insights into the brain systems underlying cognition in primates, and was a foundational step in bridging the gap between testing practices in animal and humans.

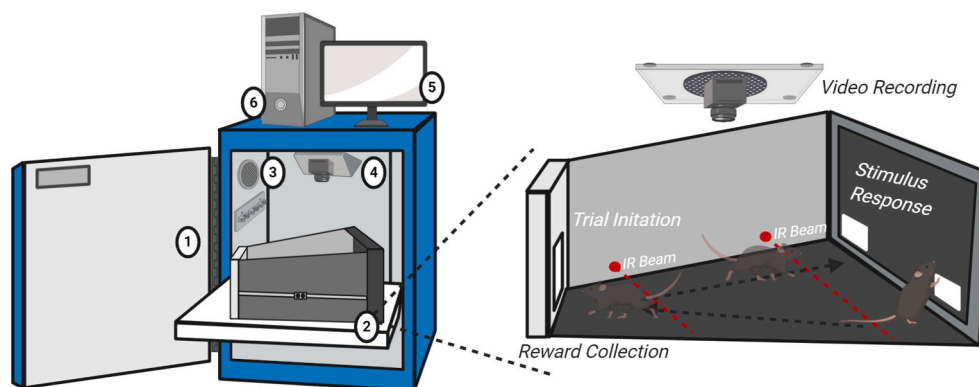
### 3.3. Touchscreen technology in rodent cognitive testing

The success of touchscreen batteries such as the CANTAB for both humans and NHPs inspired the development of a similar touchscreen-

based cognitive behavioral testing battery for rodents (Bussey et al., 1994). As noted elsewhere (Dumont et al., 2020; Hvoslef-Eide et al., 2015; Lee et al., 2020), touchscreen technology, and the expanding repertoire of available touchscreen cognitive tests (Heath et al., 2016; Horner et al., 2013; Mar et al., 2013; Charlotte A Oomen et al., 2013; Table 1 in Sullivan et al. 2020), offers several advantages that may increase replicability and the likelihood of clinical translation (Fig. 2). First, automated testing and data collection can minimize experimenter involvement during testing, which can introduce error and bias (see the example of “Clever Hans”; (Samhita & Gross, 2013)). Second, timing of responses can be reported with millisecond accuracy, increasing sensitivity to small differences between different experimental groups or manipulations. This may be especially valuable when looking for early behavioral markers of neuropsychiatric and neurodegenerative diseases in which cognitive changes may be subtle (Beraldo et al., 2019; Van Den Broeck et al., 2020). Third, stimuli and other task parameters can be varied systematically, which can be useful to probe decision-making processes and perceptual abilities of rodents (Bussey et al., 2008; Crijns & Op de Beeck, 2020; Keller et al., 2000; Mar et al., 2013; Stirman et al., 2016). This latter point is particularly relevant as sensorimotor function and vision decline with age, and can be disproportionately affected in some neuropsychiatric and neurodegenerative disorders (Chiu et al., 2012; Dutescu et al., 2009; Edwards et al., 2014; King et al., 2018; Ning et al., 2008). Fourth, touchscreen testing makes a relatively low demand on motor ability and navigation. Neurodegenerative diseases such as HD, PD, and ALS are characterized by a progressive motor deterioration in combination with cognitive dysfunction, and touchscreen systems may be more suitable for assessing cognitive decline and drug screening across the course of disease in these pre-clinical models (Heath et al., 2019; Kwak et al., 2016; Morton et al., 2006). Fifth, as mentioned above, touchscreens avoid unwanted stress which can significantly influence cognitive performance and interact with manipulations such as drugs (Cortese et al., 2019; Janickova et al., 2019). Furthermore, the hypothalamic–pituitary–adrenal (HPA) axis, which regulates glucocorticoid release in humans and rodents during stress, may be dysfunctional in diseases such as AD (Gil-Bea et al., 2010; Joshi & Praticò, 2013; Ouanes & Popp, 2019; Pomara et al., 2003). Finally, as discussed elsewhere in this review, a battery of tests conducted in rodent touchscreens can match, often almost identically, those given to human patients (Bussey et al., 2012; Heath et al., 2019; Hvoslef-Eide et al., 2015; Nithianantharajah et al., 2015; Romberg, Horner, Bussey, & Saksida, 2013b). This widens the scope of cognitive tests that can be used with a particular disease model across multiple cognitive domains within the same apparatus. This feature is particularly relevant

as some drugs may improve some cognitive deficits associated with neurodegenerative diseases, but not all. Therefore, if researchers only examine a particular process, such as memory for AD models, potential therapies that could improve other cognitive abilities (e.g., attention) may be missed (Lee, Cho, & Kim, 2020; Romberg et al., 2013b). The opposite is also true: if a drug improves one aspect of cognition, but comes with unwanted impairments in another, that too would be missed by a single-task approach. Furthermore, focusing only on one cognitive process instead of utilizing a battery approach does not mirror multifaceted clinical observations and diagnostic criteria (McKhann et al., 2011).

The advantages of rodent cognitive touchscreen testing have been capitalized upon in a number of studies of models of neuropsychiatric and neurodegenerative disease. In mouse models of AD alone, touchscreen technology has been used to examine whether amyloid plaques (e.g., APP/PS1, ArcAB, McGill-R-Thy1-APP, TgCRBD8, APP<sup>NL-G-F</sup>), tau tangles (e.g. TgTau-P301L), or both physiological hallmarks (e.g., APPSwDI/Nos2<sup>-/-</sup>, 5xFAD, 3xTgAD) contribute to the cognitive decline observed in humans (Beraldo et al., 2019; Cortese et al., 2019; Jacob et al., 2019; Kent et al., 2018; Piipponiemi et al., 2017; Romberg et al., 2011; Romberg, Bussey, & Saksida, 2013a; Romberg et al., 2013b; Shepherd et al., 2019; Van den Broeck et al., 2019). Several domains of cognition have been examined in these models including attention, response inhibition, mood, and memory (Foldi et al., 2002; Landes et al., 2001; Salmon & Bondi, 2009; Weintraub et al., 2012). Such studies often use a touchscreen ‘battery’ of tests in which responses, feedback, stimulus type, etc. are constant, thus facilitating comparison across tests (Lee et al., 2020; Shepherd et al., 2016). Touchscreen technology has been particularly useful in the study of executive functions, such as attention, working memory, cognitive flexibility and response control, which are understudied domains (perhaps due to an over-emphasis on mazes and memory; Romberg et al., 2013a). For example, the APP/PS1 mouse model of AD displayed intact sustained attention on the 5-CSRTT, but showed increased impulsivity and compulsivity when task difficulty was high (Shepherd et al., 2019). This study highlights the utility of touchscreen technology in detecting specific cognitive deficits in mouse models of neurodegenerative diseases. Recently, Beraldo et al. (2019) systematically studied three common AD mouse models longitudinally on three different touchscreen tasks: attention (5-CSRTT), cognitive flexibility (pairwise visual discrimination and reversal), and associative learning (PAL). It was observed that both the 3xTg and 5xFAD mouse models of AD showed impairments in attention and associative learning, while there was evidence that APP/PS1 mice were specifically impaired in cognitive flexibility. This study not only revealed specific cognitive



**Fig. 2.** (Left) The touchscreen testing apparatus for rodents displaying key features of the system. The sound attenuating box (1). Once the animal is placed inside the touchscreen chamber (2) the door is closed, and the animal is left undisturbed for the testing session. Speaker system (3) to deliver auditory stimuli during training. Auditory input can be used as a cue (e.g., to aid in stimulus-reward association), or as a distracting stimulus in multi-sensory paradigms. It may also be used as a task-relevant cue (e.g., auditory discrimination, etc.), if a researcher would like. A video camera (4) is located above the touchscreen chamber which provides real time video monitoring displayed on the screen (5) located on top of the system. (6) A computer system that al-

lows the experimenter to automatically start the program once the animal is inside the chamber, as well as check mouse performance parameters as the animal performs the task in real time. (Right) A schematic of the inside of the touchscreen testing chamber while an animal is performing the task, displaying the reward tray at the back (left side of the figure), the touch sensitive screen at the front (right side), and the infrared (IR) beams located near the front and the back of the chamber to detect locomotion and latency measures.

profiles across the models, but also combined and compared data across research sites using [MouseBytes.ca](#) (discussed above), showing how standardized testing combined with storage in an accessible database allows continuing meta-analyses of mouse lines as new data are added.

The neuroscientific field is constantly improving upon the generation of animal models of neuropsychiatric and neurodegenerative diseases to better recapitulate disease progression observed in humans (e.g., [Alz-Forum.org](#) and [Jax Laboratories UCI Disease Model Development & Phenotyping](#)). For example, [Saito et al. \(2014\)](#) have created a knock-in mouse model of AD by inserting common familial mutations into a humanized mouse APP gene. This mouse model develops amyloid beta plaques in the absence of overexpressing the APP gene, which better reflects human AD pathology and mitigates non-specific effects of excess APP ([Nilsson et al., 2014](#); [Saito et al., 2014](#)). Recent tests in touchscreens have found that APP<sup>NL-G-F</sup> mice can learn a visual discrimination task in touchscreens ([Jacob et al., 2019](#)), but have a variety of mild to severe impairments on tests of executive function ([Dumont et al., 2019](#)).

#### 4. Reducing the translational gap: From humans to rodents and back again

The importance of optimizing cognitive tests to assess analogous brain regions in animals and humans is highlighted in a series of experiments studying the function of the human medial temporal lobe (MTL) in visual discrimination ([Barense, 2005](#); [Lee et al., 2005](#); [Lee & Park, 2005](#)). In 1994, Eacott and colleagues used a touchscreen-based object recognition task to demonstrate that macaques with perirhinal cortex lesions displayed evidence of impaired visual perception ([Eacott et al., 1994](#)). Follow-up studies provided further evidence for this relationship, demonstrating that perirhinal lesions impaired macaque performance on touchscreen tasks designed to specifically probe visual discrimination ([Buckley et al., 2001](#); [Bussey et al., 2002](#)). Interestingly, these results would conflict with observed impairments in humans with damage to the MTL including perirhinal cortex, which suggested a primary role in recognition memory but not perception ([Buffalo et al., 1998](#); [Stark, 2000](#)). To address this discrepancy, Barense and colleagues (2005) adapted a touchscreen object discrimination task used with NHPs to assess human patients with damage to the hippocampus or general MTL (including perirhinal cortex). This experiment revealed that patients with wider MTL, but not hippocampus specific, damage were impaired when the ambiguity between visual stimuli was high, providing evidence for a role of the human MTL in visual discrimination ability. This example illustrates how standardizing behavioral tasks between species can improve animal-to-human translation.

Translation using the touchscreen testing system encompasses two related goals, to identify and study conserved mechanisms underlying cognition across species, and to improve the translational potential of pre-clinical research to human patients. A substantial focus in translational neuroscience has been the development of rodent tasks that assess analogous cognitive processes to those in humans, such as the 5-CSRTT test of attention ([Robbins, 2002](#)) and the trial-unique nonmatch-to-location (TUNL) test of working memory ([Kim et al., 2015](#); [Talpos et al., 2010](#)), or tasks that closely emulate the stimuli and task structure of human tests, such as the rodent continuous performance task ([Kim et al., 2015](#)). The benefit of this reverse translation is the availability of human patient data with which to compare the performance of an associated disease model. For example, such tests have been applied to interpreting attention and working memory ability in models of 22q11.2 microdeletion syndrome ([Nilsson et al., 2016](#); 2018) and attention deficits in models of AD pathology ([Kent et al., 2018](#); [Romberg et al., 2013b](#); [Romberg, Mattson, Mughal, Bussey, & Saksida, 2011](#)). Using the 3xTgAD mouse model of AD pathology, Romberg and colleagues (2011) were successful in identifying similar sustained attention deficits to those observed in AD patients, which were rescued following cholinesterase inhibitor administration in the same way as observed in patients. Characterizing candidate models for neurological diseases with

touchscreen task batteries is also helpful for identifying potential limitations in a model. A model may be suitable for studying the relationship between neuropathology and cognition in certain domains but may be less appropriate for others ([Nilsson et al., 2016](#), 2018).

Forward translating human touchscreen batteries (i.e., CANTAB) for rodent use has been instrumental in progressing translational neuroscience, and recent studies have worked to further refine rodent paradigms and forward translate these tasks to humans. For example, the progressive ratio (PR) paradigm used to assess motivation in rodents ([Heath et al., 2016](#); [Hodos, 1961](#)) was developed for humans as part of the EMOTICOM touchscreen battery ([Bland et al., 2016](#)). Motivational deficits are often comorbid with neurodegenerative diseases, and a recent comparison of the R6/1 model of HD and human patients on analogous touchscreen PR tasks revealed promising utility of this task for measuring apathy across species ([Heath et al. 2019](#)).

Forward translation also facilitates the progression from analogous to identical task administration across species, which may have the greatest potential to increase translation. Taking this approach, Nithianantharajah and colleagues (2015) developed a version of the PAL task that had been adapted and optimized for rodent testing and administered it to mice and humans with perturbations at the schizophrenia-related Discs Large homolog 2 (*DLG2*) gene. Both humans and mice with these perturbations were unable to learn the task and indeed, were unable to achieve much greater than chance levels of performance. Such studies provide further evidence for the conservation of the *DLG2* gene in cognition across species, and illustrate the promise of translational touchscreen testing ([Nithianantharajah et al., 2013](#); [Nithianantharajah et al., 2015](#)).

Developing identical cognitive tasks, especially vision-based tasks, for rodents and humans is not without challenges. For example, it should not be surprising that humans might require less training for some tasks compared to rodents, introducing a difference between the testing across the two species. Task parameters can, however, be varied to, for example, and bring performance of humans down from ceiling (as long as this does not compromise neurocognitive validity). Other challenges include the fact that humans can have baseline expectations when learning a task, such as the presence of an underlying rule or life experiences that transfer to (or interferes with) the task. To minimize such confounds, touchscreen tasks for humans can use neutral, non-verbal stimuli. Furthermore, human versions of touchscreen tasks are given with minimal instructions, to match the rodent task protocol. It is important to remember, however, that when we train a mouse up on, say, Trial-Unique Nonmatching-To-Location (TUNL) with no delay, we are essentially teaching the nonmatching rule to the mice before they are tested on the task proper, with delays. For humans, one could simply teach them rule verbally.

Even subtle differences between rodent and human touchscreen tasks could be a problem if the tasks are learned or performed differently (a qualitative, rather than a quantitative difference), thus compromising neurocognitive validity. However, the question of neurocognitive validity is an empirical one: we can test whether tasks recruit similar mechanisms in the two species. Such validation work needs to be supported in the quest for a successful, comprehensive mouse-to-human translational battery.

The considerations above have led to the successful cross-species testing in a number of studies ([Heath et al., 2019](#); [Nithianantharajah et al., 2015](#)). Despite these successes, however, this approach has not yet been used to realize the ultimate goal of taking a therapy (e.g., a novel compound) from pre-clinical touchscreen testing, to human testing, to use in the clinic. Nevertheless the standardized environment, protocols, and knowledge- and data-sharing, allowing more efficient and accurate screening of novel therapeutics in rodents, and the comparability of rodent and human tasks, suggests that it is just a matter of time before this goal is achieved. In the next section, we turn to a final idea that we think could accelerate successful therapeutic translation: the concept of co-clinical trials.

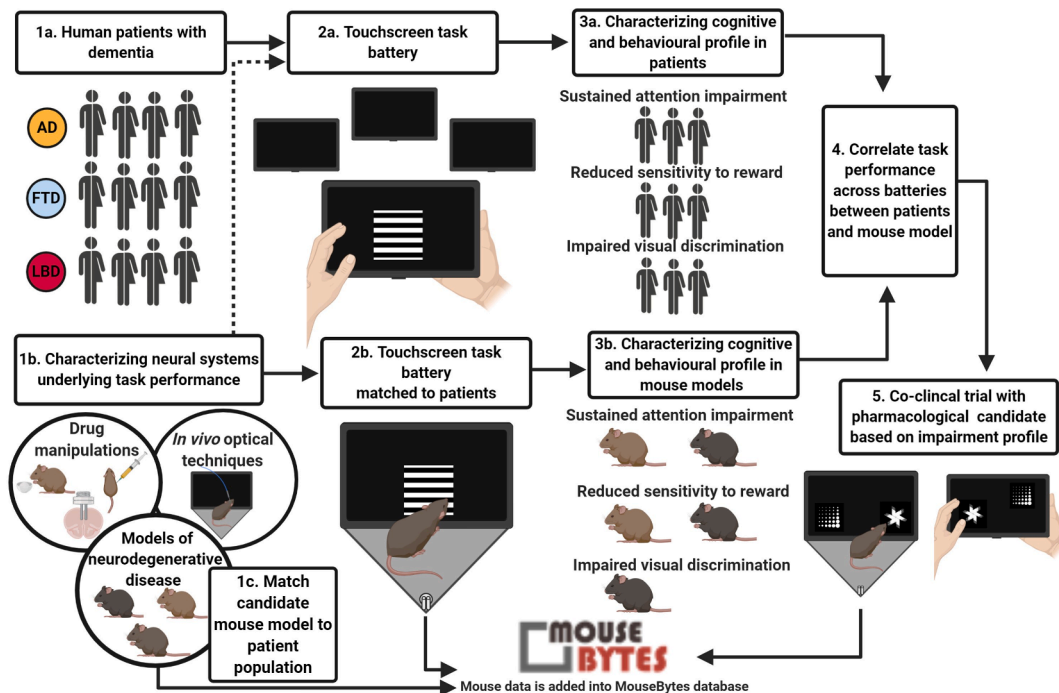
## 5. Co-Clinical trials and the future application of touchscreen research in pre-clinical and clinical research

Researchers and clinicians have been increasingly interested in developing new solutions to address the translational gap between animal and human research. Recently, several research groups across different disciplines have suggested a co-clinical trial framework for addressing the translational gap, as well as optimizing the clinical trial process (see Fig. 3). Co-clinical trial frameworks were originally proposed in the field of cancer research (Clohessy & Pandolfi, 2015; Lunardi & Pandolfi, 2015; Nardella et al., 2011). In the co-clinical framework, researchers start with a clinical population of interest and derive an animal model that recapitulates the disease of interest as closely as possible (see Fig. 3 part 1c). The researchers then decide on the main outcome measures of interest (e.g. mood inventory, cognitive task, medical diagnostic test, etc.). To maximize translational validity, the animal model and patient population are assessed with the same outcome measures (see Fig. 3 part 2a 2b). The data from the animal model and clinical population are examined, and the outcome measures with the strongest correlation are chosen for subsequent use (see Fig. 3 part 4). Once correlations in outcome measures are found between the animal and human population, the animal models can be used to rapidly screen therapeutic drugs or behavioral interventions with the most correlated outcome measures to the patient population. Finally, the insights derived from the animal screening studies can be applied immediately to the clinical population to accelerate the speed of the trial (see Fig. 3 part 5). Overall, the co-clinical process provides a framework to accelerate the clinical trial process by reducing the translational gap, identifying the most associated outcome measures, and by rapidly screening therapeutic options. Co-clinical trials could be particularly important in rare genetic neurodegenerative diseases, in which the number of simultaneously affected people is low, preventing the

development of clinical trials due to the small number of subjects.

The co-clinical framework was applied to identify new therapeutics for lung carcinomas (Kim et al., 2017), therapeutics for breast cancer (Metzger Filho et al., 2017), and cancer cell imaging (Blocker et al., 2019; Whitley et al., 2016), which has demonstrated substantial advantages to this approach over the traditional pre-clinical to clinical trial framework. The co-clinical framework is a potentially powerful tool for optimizing clinical trials in the field of neuroscience; though additional aspects unique to neuroscience require consideration. Whereas outcome measures in oncology research may be homologous in rodent and humans (i.e., measurements of tumor growth), trials in neuroscience where cognitive and behavioral outcome measures are key will require development and validation of common indices across species. Critically, the translational validity of cognitive tasks as surrogate indices of the target behavioral or cognitive symptoms in humans need to be established.

We propose the use of touchscreen-based cognitive testing in both species to standardize outcome measures in a co-clinical trial framework (see Fig. 3). This proposal represents a critical shift in the methods of clinical trials for neurodegenerative disorders. The co-clinical trial framework has not yet been used in the neurosciences, however we believe the benefits of this approach can provide substantial advantages over previous methods. Previous work has already established that mouse models and human patients with the same genetic conditions can be tested on the same cognitive tasks (Heath et al., 2019; Nithianantharajah et al., 2015; Romberg et al., 2011; Romberg et al., 2013b). Current progress is being made to further expand the human touchscreen cognitive battery with more analogs to the rodent touchscreen batteries (i.e., forward translation). If the cognitive tasks reveal a correlated impairment profile between patients and rodent models that is associated with a target symptom or deficit, researchers can establish standardized outcome measures to aid in identifying and



**Fig. 3.** Co-clinical trial development for dementia-related cognitive testing between human patients and associated mouse models. In this model, the human clinical trial patients are matched with a rodent model that recapitulates key disease pathophysiology or genetic mutation (1a and c). Choosing appropriate touchscreen tests can be guided by previous studies that have characterized the neural systems and circuits necessary for task performance (1b). b Human patients and associated rodent model populations undergo the same cognitive test battery (2 a and b). Assessing converging phenotypes between species allow researchers to identify mouse model candidates that recapitulate patient cognitive profiles (3a, b, and 4). Next, pharmacological candidates can be rapidly screened with the rodent population, with the insights directly benefitting the human trial (5). Furthermore, phenotyping various mouse models on touchscreen tests generates cognitive profiles that can be added to the [MouseBytes.ca](https://www.mousebytes.ca) database, which enables cross-site and cross-model comparisons.

selecting therapeutic candidates. Interventions can then be evaluated on selected cognitive tasks in proof of concept studies initially in rodents and then humans.

With a standardized cross-species touchscreen-based cognitive battery, we can continue to benefit from the advantages established by human touchscreen batteries such as CANTAB, while preserving cross-species translational validity. Using parallel touchscreen testing in rodents and humans (see Fig. 3, part 2a and b), we can begin to identify the core cognitive deficits that underlie the phenotypic symptoms of neurodegenerative conditions and that can be modelled in rodents. With these shared systems, we can develop highly selective batteries that will be better suited for screening novel therapeutics.

In order to further optimize the use of co-clinical trials, additional considerations should be made. The strength of co-clinical trials can be increased with the use of standardized and openly accessible behavioral protocols. To this end, the [TouchscreenCognition.org](https://www.touchscreen-cognition.org) website can provide a framework for sharing protocols and providing standardized SOPs that can reduce variability between co-clinical trial methodologies. Reduced variability in methodology will help to increase the experimental rigor to improve the ability to compare studies. Another important consideration for co-clinical trials is the collection and sharing of data. Pairing a touchscreen-based co-clinical trial with the [MouseBytes.ca](https://www.mousebytes.ca) data repository will provide a new framework for aiding collaboration, sharing research, and allowing for additional analyses on primary data (Beraldo et al., 2019).

## 6. Conclusions

The development of touchscreen technology has presented an opportunity for neuroscientists and clinicians to bridge the translational divide between human clinical research and animal pre-clinical research. Reducing the translational divide has the potential to optimize and improve the translation of findings from pre-clinical animal studies to human clinical trials. Currently the lack of translation between pre-clinical and clinical research has led to decades of failure in identifying new therapeutics for neurodegenerative disorders (Anand & Singh, 2013; Kaduszkiewicz et al., 2005; Raina et al., 2008). The lack of new treatments for these conditions suggests that a paradigm shift is necessary in order to have success. We propose that a co-clinical trial framework utilizing the strengths of touchscreen technology for both human and animal studies will help to reduce the translational divide.

Human and animal researchers can benefit from increased reliability in the clinical trial process with the use of analogous touchscreen methodologies. Touchscreen methodologies can also provide a faster approach for mass screening new drug candidates in both rodents and humans. Faster screening and increased reliability in the context of a co-clinical trial framework has the potential to significantly improve the success rates of identifying new therapeutics.

In addition to the development of touchscreen technology, the internet has provided the opportunity to develop tools to further optimize standardization, reliability, and translation. By developing open-access data repositories (e.g. [MouseBytes.ca](https://www.mousebytes.ca)), we can begin to share data rapidly between research facilities in an effort to increase rigor, replication, reduce redundancy, and identify novel insights. Additionally, providing open access to operating protocols can further enhance standardization and reliability. Overall, the integration of touchscreen methodologies with newer technology available over the internet will accelerate therapeutic discovery.

Touchscreen technology alone is not sufficient for finding better therapies. Indeed, we need to shift as a field towards newer models of clinical trials, such as the co-clinical framework. Co-clinical frameworks have been used successfully to accelerate cancer research, and by pairing it with touchscreen technology, can be used to fundamentally transform neuroscientific clinical trials. The co-clinical framework can be used to optimize discovery of treatments for conditions such as AD, FTD, PD, ALS, and many others.

## Declaration of Competing Interest

Tim Bussey and Lisa Saksida have established a series of targeted cognitive tests for animals, administered via touchscreen within a custom environment known as the “Bussey-Saksida touchscreen chamber”. Cambridge Enterprise, the technology transfer office of the University of Cambridge, supported commercialization of the Bussey-Saksida chamber, culminating in a license to Campden Instruments. Any financial compensation received from commercialization of the technology is fully invested in further touchscreen development and/or maintenance.

## Acknowledgements

This authors would like to thank BrainsCAN at Western University through the Canada First Research Excellence Fund (CFREF) and MITACS for their on-going support. LMS is a CIFAR Fellow in the Brain, Mind and Consciousness program. The authors would like to thank Hannah Bigelow for her drawings in Fig. 1. Figs. 2 & 3 were created with [BioRender.com](https://www.biorender.com).

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