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Use of Experimental Medicine Approaches for the Development of Novel Psychiatric Treatments Based on Orexin Receptor Modulation

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Declaration of interest

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Asad Malik: Full-time employee of P1vital Ltd.
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Michel Alexander Steiner: Full-time employee of, and owns shares at, Idorsia Pharmaceuticals Ltd.
Marc N. Potenza: Dr. Potenza has consulted for Opiant Therapeutics, Game Day Data, Baria-Tek, the Addiction Policy Forum, AXA and Idorsia Pharmaceuticals; has been involved in a patent application with Yale University and Novartis; has received research support from Mohegan Sun Casino and the Connecticut Council on Problem Gambling; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse-control disorders or other health topics; has consulted for and/or advised gambling and legal entities on issues related to impulsive, compulsive and addictive disorders; has edited journals and journal sections; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts

Conflict of interest statement

Dr. Potenza discloses the following. Dr. Potenza has consulted for Opiant Therapeutics, Game Day Data, Baria-Tek, the Addiction Policy Forum, AXA and Idorsia Pharmaceuticals; has been involved in a patent application with Yale University and Novartis; has received research support from Mohegan Sun Casino and the Connecticut Council on Problem Gambling; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse-control disorders or other health topics; has consulted for and/or advised gambling and legal entities on issues related to impulsive, compulsive and addictive disorders; has edited journals and journal sections; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts. Dr Coloma and Dr Steiner are full-time employees of, and own shares at, Idorsia Pharmaceuticals Ltd.
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Abstract

Despite progress in understanding the pathological mechanisms underlying psychiatric disorders, translation from animal models into clinical use remains a significant bottleneck. Preclinical studies have implicated the orexin neuropeptide system as a potential target for psychiatric disorders through its role in regulating emotional, cognitive, and behavioral processes. Clinical studies are investigating orexin modulation in addiction and mood disorders. Here we review performance-outcome measures (POMs) arising from experimental medicine research methods which may show promise as markers of efficacy of orexin receptor modulators in humans. POMs provide objective measures of brain function, complementing patient-reported or clinician-observed symptom evaluation, and aid the translation from preclinical to clinical research. Significant challenges include the development, validation, and operationalization of these measures. We suggest that collaborative networks comprising clinical practitioners, academics, individuals working in the pharmaceutical industry, drug regulators, patients, patient advocacy groups, and other relevant stakeholders may provide infrastructure to facilitate validation of experimental medicine approaches in translational research and in the implementation of these approaches in real-world clinical practice.

Keywords

Orexin antagonist; Orexin agonist; Orexin system; Experimental medicine; Performance-outcome assessment; Cognitive task; Drug development; Psychiatry; Clinical trial

1. Introduction

There is an unmet clinical need concerning many aspects of the treatment of neuropsychiatric disorders. This is the case for disorders where current treatments already exist, like depression and anxiety disorders, and for those where pharmacological treatments are limited, such as substance use disorders (SUDs), and other disorders characterized by compulsive behavior, including eating disorders. The increasingly high prevalence and cost of these psychiatric disorders (McCrone et al., 2008; OECD, 2018; Substance Abuse and Mental Health Services Administration, 2021; The Lancet Global Health, 2020) lends urgency to the search for new treatments and raises questions about the best methodological approaches to determine their efficacy.

The orexin neuropeptide system has emerged as a potential new drug target for neuropsychiatric conditions. Although a primary function of orexin is the stabilization of wakefulness, animal studies have demonstrated that it also influences emotional, cognitive, and behavioral processes, including stress responsivity, reward processing, motivation, and feeding (Baimel et al., 2015; Boutrel et al., 2005; Harris et al., 2005; Haynes et al., 2000; Mahler et al., 2012; Tisdale et al., 2021). In humans, genetic association studies have supported links between the orexin system and specific psychiatric illnesses (Cengiz et al.,

2019; Hollander et al., 2012; Nishino and Yoshida, 2003; Nishizawa et al., 2015). However, investigation of the orexin system beyond sleepwake regulation in clinical research is still at an early stage.

The orexin system's role in diverse brain functions makes it an interesting example to illustrate how performance outcome paradigms can inform therapeutic indications for the focus of future research efforts. Performance outcomes yield measurements of physical or cognitive function, via the participant's completion of a task according to specific instructions (Richardson et al., 2019). This can include physical tasks, such as timed walking, and/or those involving wearable technology. Another class of performance outcomes includes neuropsychological assessments that capture measurements related to cognition, perception, or decision-making, and may involve computerized testing. Traditionally these tests have been used in the laboratory and fall within experimental medicine approaches (Koychev et al., 2010). Their use in clinical research has been predicated on the notion that the resulting measures capture aspects of brain function which may otherwise be challenging for individuals to subjectively report or clinicians to observe.

This review critically evaluates experimental medicine approaches for clinical development of orexin receptor modulators as potential new treatments for some psychiatric conditions. We include a synthesis of the areas of cognition and perception in which the orexin system has been implicated, with a summary of the cognitive tasks that may be promising in evaluating the effects of orexin receptor modulation in humans. We focus on paradigms with simple technological requirements and/or limited ethical challenges for their implementation since these are likely to be applicable at multiple stages of clinical drug development. Hence, neuroimaging approaches, or those that rely on procedures such as eye tracking or administration of substances with abuse potential, are out of scope. Lastly, we summarize key challenges in the use of performance outcomes to support their use in clinical studies, drug registration, and marketing authorization.

2. Overview of the orexin system

Orexins are excitatory neuropeptides produced by neurons in the perifornical area and the dorsomedial and lateral hypothalamus (LH), and their release from extensive projections of these neurons throughout the central nervous system is triggered by a variety of factors (Date et al., 1999; de Lecea et al., 1998; Peyron et al., 1998; Sakurai et al., 1998). Orexins are also known as hypocretins, which denotes their localization to cell bodies in the hypothalamus and the sequence homology with the gut peptide secretin. The two peptides termed orexin-A and orexin-B are derived by proteolytic processing from a common precursor protein called prepro-orexin, which is highly conserved across mammalian species (Soya and Sakurai, 2020). These peptides bind to and activate orexin type 1 (OX1R) and type 2 (OX2R) G-protein-coupled receptors that are expressed widely throughout the brain, consistent with a role in multiple physiological functions (Fig. 1). OX1R was shown to have a slightly greater affinity, about one order of magnitude, for orexin-A over orexin-B, whereas OX2R binds both ligands with similar affinities (de Lecea et al., 1998; Hong et al., 2021; Sakurai et al., 1998). We note, though, that these measurements were based on OXR expression and signaling in recombinant systems, which complicates a direct,

quantitative comparison of ligand affinities. It might well be different in native systems (Kukkonen, 2013). OX1R and OX2R show partially overlapping expression, although some brain regions preferentially express one receptor subtype over the other. For example, OX1R appears to be selectively expressed in the locus coeruleus and cingulate cortex, while OX2R is predominantly found in the tuberomammillary nucleus, hypothalamic paraventricular nucleus, and nucleus accumbens (NAc) (Marcus et al., 2001; Matsuki and Sakurai, 2008; Mieda et al., 2011).

2.1. Multiple physiological functions

Orexin neurons stabilize wakefulness, regulate rapid eye movement sleep physiology, and are primarily active during wakefulness (Kantor et al., 2009; Lee et al., 2005; Mieda et al., 2011; Mileykovskiy et al., 2005; Sakurai, 2007). Orexin-A is released from synaptic sites during wakefulness and sleep deprivation (Blouin and Siegel, 2013; Zeitzer et al., 2003). The discovery that human narcolepsy involves selective loss of orexin neurons led to advances in understanding this condition (Mahoney et al., 2019; Nishino et al., 2000; Peyron et al., 2000; Thannickal et al., 2000), and similar findings have been observed in other mammalian species (Chemelli et al., 1999; Lin et al., 1999; Sakurai, 2013; Tisdale et al., 2021). A potential role for orexin in feeding regulation was suggested by the finding that orexin neurons are localized in the tuberal hypothalamus, a region involved in control of feeding behavior (Sakurai et al., 1998). Also, intracerebroventricular administration of orexins during the light period promotes feeding behavior in rats and mice (Haynes et al., 2002; Haynes et al., 2000; Sakurai et al., 1998; Yamanaka et al., 2000), although this could be due, at least partially, to increased wakefulness of the animals. Orexin-deficient mice, on the other hand, exhibit reduced food consumption (Hara et al., 2005; Willie et al., 2001) and studies in food-deprived rats showed that hypothalamic orexin neuronal activity was increased in response to conditioned cues, including expectation of receiving palatable chow (Choi et al., 2010; Harris et al., 2005; Petrovich et al., 2012).

Orexin neurons project from the LH to mesolimbic reward pathway areas, including the ventral tegmental area (VTA) and NAc, which are involved in behavioral responses to drugs of abuse. In line with this anatomical distribution, a role for orexins was established in regulation of motivated, emotional, reward-seeking, and addictive behaviors (Baimel et al., 2015; Boutrel et al., 2005; Harris et al., 2005; Mahler et al., 2012; Yamanaka et al., 2003). Orexin neurons are found in brain regions such as the central nucleus of the amygdala and the bed nucleus of the stria terminalis, which are associated with fear and anxiety-related behaviors. Other studies have provided evidence for a role for the orexin system in emotion, consolidation of emotional memory, anxiety, and panic-like behaviors (Chung et al., 2014; Johnson et al., 2012; Johnson et al., 2010; Li et al., 2010; Soya et al., 2013; Steiner et al., 2012). Associations between orexin neuronal activity and behavioral, neurocrine, and physiological responses to acute stress have been investigated widely and are reviewed elsewhere (Giardino and de Lecea, 2014; Sargin, 2019).

2.2. Interactions with multiple neurotransmitter systems

The role of the orexin system in sleep/wakefulness has been proposed to occur via modulation of multiple downstream arousal-promoting brain nuclei (Fig. 1). The LC

receives dense extrahypothalamic projections from orexin neurons (Date et al., 1999; Hagan et al., 1999), which modulate activity of noradrenergic neurons and stimulate co-release of the excitatory neurotransmitter glutamate (Henny et al., 2010; Sears et al., 2013). In addition, orexin-A and orexin-B increase firing of serotonergic neurons in dorsal raphe nuclei and local inhibitory GABAergic input to serotonergic neurons (Brown et al., 2001; Liu et al., 2002), which, in turn, send abundant projections to pedunculopontine and laterodorsal tegmental nuclei, substantia nigra and amygdala (Sakurai, 2007). VTA dopaminergic neurons also contribute in regulating vigilance and attention (Eban-Rothschild et al., 2016; Yu et al., 2019), with modulation via arousal-related neurotransmitters such as glutamate, serotonin, and acetylcholine (Oishi and Lazarus, 2017). GABAergic neurons in the VTA become quiescent during waking, directly inhibiting LH orexin neurons (Chowdhury et al., 2019). Furthermore, activation of the orexin-basal-forebrain pathway stimulates acetylcholine release and cortical neuronal activity, contributing to attention processing with arousal (Fadel and FrederickDuus, 2008; Villano et al., 2017), and glutamatergic and GABAergic projections to LH orexin neurons further contribute to wakefulness, motivation, and other behaviors (Agostinelli et al., 2017). The importance of orexin signaling in reinforcement and reward-related processes via actions on VTA-dopamine neurons has been demonstrated in various studies, including morphine (Richardson and Aston-Jones, 2012; Taslimi et al., 2012) and cocaine (Bernstein et al., 2018; Espana et al., 2011; Espana et al., 2010) preference in self-administration animal models. Serotonergic neurons in the dorsal raphe are also active in expected/unexpected reward stimuli, including those for food, sex, and social interaction in mice (Li et al., 2016). This pathway appears to operate synergistically with the orexin-VTA pathway in modulation of reward/addiction (Li and de Lecea, 2020). Orexin neurons also project to the paraventricular thalamus which, in turn, projects to the NAc, bed nucleus of the stria terminalis, and amygdala, suggesting a role in modulation of reward/addiction processing, cognition, stress, and anxiety (Hamlin et al., 2009; Huang et al., 2006; Kirouac, 2015; Li et al., 2010). A role for orexinergic innervation in hedonic behavior is highlighted by the dense projections of orexin neurons to the ventral pallidum, a region involved in modulation of motivated behavior (Ch'ng and Lawrence, 2015; Ho and Berridge, 2013; Root et al., 2015). Other brain regions innervated by orexin neurons include: 1) insular cortex, which appears to contribute to amplification of orexin signaling in hedonic valence processing via GABAergic neurotransmission (Castro and Berridge, 2017); 2) arcuate nucleus, which mediates feeding and body-weight regulation via reciprocal orexin and neuropeptide Y connections (Fu et al., 2004; Muroya et al., 2004); and 3) local circuits within the hypothalamus containing glutamatergic and GABA-ergic neurons (Li and de Lecea, 2020).

3. Orexin receptor modulators for treatment of psychiatric disorders

More than 20 orexin receptor antagonists have been investigated in both preclinical and clinical studies for multiple indications. The dual OX1R/OX2R antagonist (DORA) almorexant was one of the first members of this new class of drugs, with sleep-promoting effects demonstrated in rats, dogs, and humans (Brisbare-Roch et al., 2007). In healthy volunteers, almorexant induced sleepiness without impairments in memory or cognitive functioning (Neylan et al., 2020). Although clinical development of almorexant was

discontinued because of non-target-related safety concerns, three DORAs, suvorexant, lemborexant, and daridorexant were approved in the last decade by the US Food and Drug Administration (FDA) for the treatment of insomnia. Daridorexant is also, in 2022, the first DORA to be authorized in Europe. While the preclinical evidence has pointed to a potential role for the orexin system in feeding behavior, none of the large, longer-term clinical phase III trials involving the three FDA-approved DORAs has shown any effect on body weight (Kunz et al., 2023; Michelson et al., 2014; Yardley et al., 2021). Other DORAs such as YZJ-1139 and TS-142, as well as the selective OX2R antagonist (SO2RA) seltorexant and the selective OX1R antagonists (SO1RAs) JNJ-61393215 and ACT-539313, are in clinical phase 2 and 3 trials. As of August 2022, there are 53 completed, and 27 ongoing, clinical studies of orexin modulators registered in clinialtrials.gov. In addition to sleep disorders, potential indications such as SUDs, other addictive disorders, eating disorders, anxiety/panic disorders, and depression have received significant attention. While DORAs and SO2RAs promote sleep and should be preferentially administered at night-time, SO1RAs are largely devoid of sleep-promoting effects and can be administered during the day.

The therapeutic use of orexin receptor agonists, particularly OX2R agonists in the treatment of narcolepsy, has been supported by preclinical studies (Irukayama-Tomobe et al., 2017; Yukitake et al., 2019) and a phase 1 study of danavorexton (TAK-925) in patients with narcolepsy type 1 (NT1) showed increased wakefulness compared to placebo (Evans et al., 2019). Another OX2R agonist, TAK-994, was under investigation for excessive daytime sleepiness in NT1 and received breakthrough therapy status from the FDA in July 2021. However, the phase 2 study was stopped due to safety issues (Takeda Pharmaceutical Company Limited, 2021).

The wide-ranging therapeutic potential of orexin receptor modulators and early-stage exploration in psychiatric indications make them a strong candidate to examine experimental medicine approaches to facilitate investigation of efficacy signals.

4. Experimental medicine and neurocognitive approaches

Experimental medicine (also called translational medicine) refers to studies in humans aimed at identifying disease mechanisms of action or demonstrating proof-of-concept for new discoveries or treatments (The Lancet, 2012; UK Research and Innovation, 2022). In the study of psychiatric disorders, such approaches may employ tasks that rely on specific brain circuits assumed to be modulated by compounds of interest. Thus, patients' performance on these tasks may serve as indicators of the effects of new treatments on the underlying disease process rather than an effect on symptoms (Fig. 2) (Dawson and Goodwin, 2005). These performance-outcome measures (POMs) are often based on standardized tasks actively undertaken by a patient according to a set of instructions and may be administered by an appropriately trained individual or completed by the patient independently.

POMs comprise one category of clinical outcome assessments (COAs) considered by health authorities in evaluations of clinical efficacy of new drugs. COAs include patient-, observer-, and clinician-reported outcome measures. Observer-reported measures reflect observable

signs, events, or behaviors from someone other than the patient or healthcare provider, such as a parent or caregiver). Advantages of POMs are given in Box 1.

Arguably the most advanced area of experimental medicine approaches showing the potential of POMs in psychiatric research has centered on emotional processing biases in depression and the effect of antidepressants in shifting these patterns. Several studies have shown that antidepressants can reduce processing of negatively-valenced stimuli and/or enhance processing of positive stimuli in healthy, depressed, and at-risk groups (Godlewska and Harmer, 2021; Harmer, 2013; Harmer et al., 2017; Warren et al., 2015). Importantly, treatment-induced changes in emotional processing may occur within days of drug administration, preceding the amelioration of depressive symptoms which usually take weeks to emerge with commonly prescribed antidepressants. Additionally, some studies have suggested that shifts in emotional processing may be predictive of the degree of symptom amelioration (Dawson et al., 2021; Shiroma et al., 2014; Tranter et al., 2009). POMs can also be used to distinguish individuals who have the pathologic behavior reflecting the disorder of interest from those who do not have it and may help identify patients who are more likely to respond to targeted therapy. Together, these findings support the potential of experimental medicine approaches to provide drug-efficacy signals which may: 1) reflect mechanism of action; 2) emerge early in the treatment course; and 3) provide a basis for defining treatment responders, informing personalizedmedicine approaches.

As an example of the above potential benefits, phase 1 studies in healthy participants assessing the pharmacodynamic effects of an investigational drug could incorporate POMs covering a range of cognitive and processing domains. Data emerging from such trials could inform decisions about appropriate indication(s), as well as enrollment criteria for later studies. In subsequent phase 2 or phase 3 studies, POMs may complement established indicators of efficacy in clarifying effects of compounds on cognition or other relevant functions. For example, clinical trials assessing SO1RA/SO2RA and DORA compounds have typically included at least one sleep assessment due to associations with the orexin system. Inclusion of POMs early in the clinical development of such compounds may identify rapid-onset effects on performance outcomes as a potential early predictor of treatment response. They may also inform whether symptom improvement is secondary to better sleep or a direct effect on the measured cognitive/perceptual domains, particularly when longitudinal collection of performance-outcome data is done. Moreover, such approaches could also identify potential markers of sustained response.

Within the last decade, transdiagnostic approaches have been put forward to enable better understanding and treatment of mental illnesses (Cuthbert, 2014; Cuthbert and Insel, 2013; Insel, 2014; Morris and Cuthbert, 2012). Experimental medicine methodologies fit well with transdiagnostic approaches because they involve indexing aspects of cognition that are relevant across the entire spectrum of human behavior, both in health and disease. Deviations from a normative behavioral pattern may be evident in multiple disorders, providing potential transdiagnostic cognitive targets. At the same time, the same aberration in cognitive or behavioral measures may also arise via different mechanisms where the condition is known to be heterogeneous, as is the case for most psychiatric disorders. One example of research in this vein has been the recent focus on anhedonia. Anhedonia is

characterized by difficulties in experiencing or seeking pleasure and is a feature of multiple psychiatric disorders including depression and schizophrenia (Husain and Roiser, 2018; Šagud et al., 2019; Treadway and Zald, 2011). Anhedonia may be assessed via interviews or questionnaires, but tasks that measure willingness to exert effort to earn rewards have also been developed, providing objective performance-outcome results (Green et al., 2015). Of note, performance outcomes derived from an effort-based decision-making task were collected as secondary outcome measures in a phase 4 randomized controlled trial of the antidepressants vortioxetine and desvenlafaxine (NCT04448431; discussed in more detail below) (Clinicaltrials.gov, 2022g).

5. Experimental medicine paradigms and development of orexin receptor modulators for psychiatry

There are several questions to consider when using experimental medicine approaches with cognitive POMs in intervention studies (Box 2). Below, we address these questions to determine the most relevant and promising performance outcomes for development of orexin receptor modulators in psychiatric disorders. We focus on paradigms suitable for both small and large clinical trials, with the latter possibly requiring simpler implementation. The paradigms are organized according to the cognitive or psychological domains that they are intended to measure and highlight key preclinical work that supports the case for involvement of the orexin system.

5.1. Reward processing

Human reward processing is recognized as a multidimensional construct and likely involves distinct neural mechanisms. The National Institute of Mental Health research domain criteria differentiate between three aspects of reward processing (responsiveness, learning, and valuation), each of which is associated with multiple subdomains. For example, subdomains of reward valuation include response to delay and willingness to exert effort for rewards. Many existing human paradigms designed to measure reward processing rely on neuroimaging or EEG endpoints which can be more technically challenging, and these are discussed elsewhere (Balodis and Potenza, 2015; Meyer et al., 2021). Considering the role of the orexin system in motivated behaviors and reward-seeking, the US National Institute on Drug Abuse identified orexin receptor modulation as a high priority target for development of new medications for opioid use disorder (Rasmussen et al., 2019). In line with this, several preclinical models have been used to investigate the role of different orexin receptor antagonists in drug-seeking/drug-taking behaviors (Aston-Jones et al., 2010; Baimel et al., 2015; Plaza-Zabala et al., 2012).

5.1.1. Effort to attain rewards—Preclinical evidence supports a role for the orexin system in mediating behavior towards highly motivational reinforcers, including amount of effort expended in pursuit of rewards, such as drugs of abuse and palatable food (Baimel et al., 2015; Boutrel et al., 2013; Brodnik et al., 2015; Brown et al., 2022; Cason et al., 2010; Espana, 2012; Muschamp et al., 2014). A key paradigm which indexes effort made to attain rewards is the progressive ratio task (Roane, 2008). In human and animal versions of this task, the subject makes a sequence of effortful responses (e.g., button presses) to

earn a reward. Following delivery of the reward, the number of responses required to earn subsequent rewards is increased and this continues until the participant stops responding. The schedule for the responses required to earn the reward varies but is typically increased linearly or exponentially. The key endpoint of the task is the cessation of responses.

The progressive ratio task has been used extensively for evaluating the reinforcing efficacy of drugs of abuse in preclinical studies (Stafford et al., 1998), including investigations of orexin receptor modulators on drug-seeking behavior. For example, systemic administration of the SO1RA SB-334867 compound had no effect on cocaine self-administration under fixed ratio (FR)1 or FR3 schedules of reinforcement (Smith et al., 2009). However, Hollander et al. found decreased responses for cocaine following a higher-demand FR5 schedule and by genetic deletion of OX1R (Hollander et al., 2012). Furthermore, systemic or intra-VTA injections of SB-334867 decreased the maximal effort animals expended under a progressive ratio schedule (Borgland et al., 2009; Brodnik et al., 2015).

An important challenge that comes with these reward-based paradigms is their use in large clinical trials involving administration of rewards such as substances of abuse. A recent small study of suvorexant in cocaine use disorder, employing a progressive ratio task to measure the reinforcing effects of cocaine, showed that suvorexant maintenance increased motivation to choose cocaine over money in humans (Stoops et al., 2022). These findings are incongruous with previous preclinical literature showing orexin antagonism attenuates the reinforcing and other abuse-related effects of cocaine. Rat studies have previously shown that DORAs can reduce operant responding for cocaine under a progressive ratio schedule (Gentile et al., 2018a; Prince et al., 2015). It should be noted, though, that suvorexant was given to the subjects in the human study sub-chronically, and before bedtime, while the behavioral assessments were done the next morning. Contrarily, all reported animal experiments administered the orexin antagonists acutely, directly before testing.

Effort-based decision-making tasks (EBDMTs) have emerged recently as another paradigm to measure willingness to work for rewards (Fig. 3) (Chong et al., 2016; Massar et al., 2018). In clinical studies employing EBDMTs, the participant chooses between difficult and easy (sub)tasks. If the participant completes their chosen task, a reward of variable value (e.g., monetary), and sometimes variable probability, is available. Analytic approaches for the tasks vary but all aim to estimate the influence of reward magnitude, reward probability, and/or expected value on choice behavior. This can be computed using a generalized estimating equation (Treadway et al., 2009) or by calculating the proportion of hard choices for each condition of interest, such as each reward level (Reddy et al., 2015).

EBDMTs may require participants to invest motor or cognitive efforts (Culbreth et al., 2016; Reddy et al., 2018; Treadway et al., 2009). Their ecological validity is supported by data showing associations between task-performance outcome and anhedonia (Culbreth et al., 2020a; Culbreth et al., 2020b; Horan et al., 2015). The most widely used EBDMT is the effort expenditure for rewards task (EEfRT), which assesses willingness to exert motor effort (in the form of button presses) for variable monetary rewards available at different probabilities (Treadway et al., 2009). Effort-based decision-making paradigms have been used to investigate treatments for disorders characterized by motivational dysfunction, such

as major depressive disorder (MDD), schizophrenia and Parkinson's disease (Green et al., 2015; Reddy et al., 2015; Salamone et al., 2018; Salamone et al., 2016). EBDMTs have been used in other indications, including those for which orexin receptor modulators may be useful. For example, Stuppy-Sullivan and Baskin-Sommers found that individuals with severe SUD displayed decreased sensitivity to expected value information when choosing between hard and easy tasks in the EEfRT for monetary rewards. Individuals whose severity of SUD severity was related to avoiding aversive affective states were the least sensitive to expected value signals (Stuppy-Sullivan and Baskin-Sommers, 2019).

In addition to the evidence for the use of EBDMTs in SUDs, they have also been used in other indications in which orexin has been implicated. Microinjection experiments have supported a role for the orexin system in promotion of feeding, and this primarily occurs via orexin-A and OX1Rs. Recent evidence suggests that the orexin system is not indiscriminately linked to feeding but underlies seeking and consumption of palatable foods, food-seeking motivated by hunger, or seeking elicited by conditioned stimuli (Borgland, 2019; Cason and Aston-Jones, 2014; Mahler et al., 2012; Piccoli et al., 2012). Animal models have shown high levels of orexin following caloric deprivation or binge-like eating (Castro et al., 2016; Karteris et al., 2005; Olszewski et al., 2009; Thorpe et al., 2005). Moreover, orexin stimulates eating and willingness to work for palatable food (Choi et al., 2010; Valdivia et al., 2015). In an eating-disorder study, Racine et al. used a modified version of the EEfRT to examine willingness to work for food reward in individuals with binge eating disorder (BED). Participants with higher BED severity were driven more strongly by food reward, compared to those with low binge-eating levels (Racine et al., 2018).

Together, these findings suggest that EBDMTs may represent valuable POMs in psychiatric conditions, including those where response to reward is dampened (e.g., anhedonia) as well as conditions where incentive salience of the reward appears to be amplified (as may be the case with food in BED). Test-retest data for several EBDMTs have been reported as good to excellent in a schizophrenia study (Reddy et al., 2015). Other data support EBDMTs' sensitivity to drug effects. For example, Wardle et al. showed that d-amphetamine administration enhanced willingness to exert effort for monetary rewards among healthy volunteers completing the EEfRT, particularly when reward probability was lower (Wardle et al., 2011). A study on acute effects of cannabis with and without cannabidiol found that the latter reduced likelihood of high-effort choices relative to placebo and increased sensitivity to expected reward value (Lawn et al., 2016). The EEfRT has been used as a secondary outcome measure in a recent phase 4 randomized controlled trial investigating the effects of vortioxetine versus desvenlafaxine in individuals with MDD and partial response to selective serotonin reuptake inhibitor monotherapy (NCT04448431) (Clinicaltrials.gov, 2022g). Results demonstrated non-inferiority of vortioxetine vs. desvenlafaxine on the primary study endpoint (Montgomery–Åsberg Depression Rating Scale [MADRS] total score) with benefits for vortioxetine in secondary endpoints including remission, daily and social functioning, and satisfaction with medication (Nordic Life Science News, 2022). Including the EEfRT in this study design may prove valuable in enabling investigators to examine drug effects on effortful choice as a complement to a clinician-rated index of

anhedonia (MADRS anhedonia factor score) and potentially in relation to other collected measures of general cognition, function, and quality of life.

Implementation of EBDMTs raises several practical issues. While some versions of the task do not require specialist hardware, some do, such as devices used to measure grip force reflecting motor effort (Reddy et al., 2015), these may not be readily available at the clinical sites chosen for a study. Finally, it should be considered that most EBDMTs are >20 minutes in duration and may therefore result in participant fatigue. Further implementation issues that are relevant across reward processing tasks are highlighted in Box 3.

5.1.2 Delay of rewards—Delay discounting, or preference for smaller, more immediate rewards over larger, delayed rewards, represents an important aspect of how rewards are valued with respect to time and is considered a type of impulsivity (sometimes termed choice impulsivity). Higher levels of delay discounting have been linked to conditions such as SUDs, gambling disorder, BED, and obesity (Bickel et al., 2012; Carr et al., 2021; Chamorro et al., 2012; Davis et al., 2010a; Hamilton and Potenza, 2012; Kollins, 2003; Leeman and Potenza, 2012; Madden et al., 2011; Moeller et al., 2001). The findings of orexin-mediated effects on VTA dopamine neurons and orexin modulation in animal models of SUDs and BED raises the possibility that the orexin system may be involved in manifestation of impulsive behaviors. However, only one preclinical study has so far investigated orexin-receptor modulation on delay discounting, with no effect found in rats treated with suvorexant or OX1R- or OX2R-selective compounds (Gentile et al., 2018b). A small recent clinical study conducted on participants with cocaine use disorder found no effect of suvorexant maintenance in a five-trial delay-discounting task measuring discounting rates for cocaine and money (Stoops et al., 2022). Nevertheless, the relationship between orexin function and impulsivity requires further research, and use of delay-discounting and other choice-impulsivity paradigms may be important in these studies.

Delay discounting is typically assessed through behavioral inter-temporal choice tasks (ITCTs) in which the subject makes a series of choices between a smaller reward delivered quickly and a larger reward delivered after a delay. Greater degrees of discounting of larger, delayed reward reflect greater choice impulsivity. From these tasks, several endpoints can be derived, including indifference points between options, area under the curve, and percent choice of large or small rewards. Numerous ITCTs exist and include protocols which use adjusting regimes, whereby choices for smaller-sooner over larger-later rewards result in adjustment of subsequent options until an indifference point is reached (Richards et al., 1999), or where actual choice consequences are experienced (Reynolds and Schiffbauer, 2004). Some studies have implemented ITCTs with hypothetical rewards while others have delivered real rewards during or following the task. ITCTs can be employed with a variety of rewards or commodities to be discounted (e.g. money, food, or substance of abuse). Readers are referred to an in-depth review on delay discounting (Hamilton et al., 2015c).

The type of reward must be determined *a priori* (Box 3) as this may have impact on choice behavior and/or disease specificity. Even though most studies offer monetary rewards, particular scenarios may require other types such as food or drugs that are more specific

to a disorder. Monetary rewards may have greater transdiagnostic potential though and are thus perhaps chosen for many studies.

5.2. Craving

Craving is a diagnostic criterion for SUDs (DSM-5) and also a feature of behavioral addictions, such as gambling and gaming (Yau and Potenza, 2015). While back-translation of craving from human to preclinical work is inexact, animal studies have demonstrated associations between decreased orexin activity and attenuation of drug-seeking and cue-reactivity (Bentzley and Aston-Jones, 2015; James et al., 2019; Steiner et al., 2018). This indicates that orexin modulation may reduce craving in humans and serve in treatment of SUDs and other addictions. Paradigms have been developed for performance outcomes related to craving, although the few clinical studies investigating effects of orexin receptor modulators on craving (e.g., NCT04229095, NCT03999099) have so far relied on subjective outcome measures (Clinicaltrials.gov, 2022d, e). In one small randomized controlled trial, Suchting et al. explored effects of treatment for two weeks with suvorexant versus placebo in individuals with cocaine use disorder, including effects on self-reported questionnaire scores and outcomes related to sleep, stress, and attentional bias (Suchting et al., 2020). The results suggested that suvorexant treatment reduced craving over time. This finding was supported by another randomized, double-blind, placebo-controlled clinical trial that demonstrated reduced craving on a subjective VAS in suvorexant-treated patients with opioid use disorder during buprenorphine taper (Huhn et al., 2022). In another, ongoing, small (N=20) randomized clinical trial, the effects of suvorexant versus placebo are currently being investigated in tobacco use disorder, including use of visual analogue scale measures of craving (NCT04234997) (Clinicaltrials.gov, 2022f).

5.2.1. Approach-avoidance tasks (AATs)—In experimental paradigms related to craving, the approach-avoidance task (AAT) measures approach versus avoidance of disease-relevant or otherwise valenced stimuli. Participants are instructed to make one type of response in reaction to images with one characteristic and to respond to images with another characteristic in a different, usually opposite, way (Fig. 4). For example, responses can be made by pulling or pushing a joystick depending on whether an image is oriented vertically or horizontally. The image size increases or decreases in response to pull or push, simulating approach or avoidance, respectively. Key POMs for a typical AAT are derivations of approach bias values, based on median reaction times. Typically, researchers derive approach bias as the difference in median reaction times between push vs. pull trials for a given stimulus category. This can be used as an outcome measure computed using only disease-relevant stimuli or contrasted between disease-relevant and non-disease-relevant stimuli (Brockmeyer et al., 2015; Sklenarik et al., 2020; Sklenarik et al., 2019; Wiers et al., 2009). In some analyses of AAT data, poorly performing participants, and/or poor-performance trials, are removed from further analysis, although working definitions of poor performance have not always been consistent across publications (Brockmeyer et al., 2015; Wiers et al., 2009). This perhaps highlights the variability that can affect some POMs and points to the need for addressing inconsistencies in analysis approaches prior to implementation in clinical trials.

AATs have provided empirical evidence that systematic biases in approach and avoidance tendencies may underlie unhealthy behaviors, with greater approach biases to stimuli associated with cravings observed among individuals with addictive or compulsive disorders. For example, individuals with active tobacco use disorder have been shown to demonstrate greater approach bias for smoking cues than individuals with remitted tobacco use disorder and those who never smoked (Wiers et al., 2013), whilst participants with high levels of food craving were shown to demonstrate stronger approach tendencies towards food than those with low levels of food craving (Brockmeyer et al., 2015). Problematic pornography use, compared with non-problematic use, was associated with more than double the approach bias towards erotic stimuli among college-aged heterosexual males (Sklenarik et al., 2019), with similar findings in college-aged heterosexual females (Sklenarik et al., 2020). Supporting the ecological validity of the task are observations that approach bias correlates with self-reported craving or change in levels of craving from pre- to post-cue exposure (Brockmeyer et al., 2015; Wiers et al., 2013).

The AAT has also been used to explore approach and avoidance of social stimuli in individuals with social anxiety disorder. For example, Heuer et al. showed that highly socially anxious individuals had stronger avoidance tendencies than non-anxious individuals towards smiling and angry faces (Heuer et al., 2007).

Although joysticks can be used to measure push versus pull responses in AATs, this can introduce technical complexities as these are not typically designed for use in clinical research. Some studies have described touch-screen AATs but there are only limited data to assess the validity of this approach (Kahveci et al., 2020; Meule et al., 2020). Occasionally divergent results have been shown when different response devices are used, highlighting the need for further investigation into effects of task versions (Brockmeyer et al., 2015; Kahveci et al., 2020). Personalised versions of the task, where bespoke selections of stimuli are implemented according to individual craving profiles, may yield more sensitive and predictive measures but poses additional implementation complexity (Kahveci et al., 2020). Even without the use of bespoke stimulus sets, there can be issues around stimulus selection and validity, as described in Box 4.

5.2.2. Regulation of craving (ROC) tasks—In contrast to AATs, regulation of craving (ROC) tasks measure cognitive downregulation and upregulation of craving. In this task, participants are presented with disease-relevant images (e.g., paraphernalia associated with substance abuse) and told to either downregulate or upregulate craving induced by the stimuli using cognitive reappraisal techniques. For example, when exposed to tobacco cues, individuals who smoke may be asked to consider how good consuming the pictured product might make them feel (upregulation) compared to the negative health impacts (downregulation). Sometimes a ‘just look’ condition is included as a no-regulation control (Sun and Kober, 2020). After each image is presented, participants are asked to rate how much they craved the item in the image on a scale from 1 (not at all) to 9 (very much). The key endpoint is the average rating of craving by regulation condition. Some researchers have also reported ‘regulatory success’, or the percent difference in averages of craving between strategy conditions and the look condition (defined as $Look\text{-}Regulate / Look$) (Boswell et al., 2018).

Several studies have demonstrated that ROC-related cognitive strategies impact craving in both healthy subjects and those who take substances of abuse or desire excessive food (Boswell et al., 2018; Giuliani et al., 2013; Kober et al., 2010; Strickland et al., 2016; Suzuki et al., 2020). Naqvi et al. found that individuals who drink socially compared to those with alcohol use disorder (AUD) were approximately twice as effective at reducing their alcohol craving in an ROC task. This suggested that AUD is associated with difficulties in regulating cue-induced craving (Naqvi et al., 2015). Wu et al. found that participants with internet gaming disorder had difficulty regulating gaming- and food-related craving (Wu et al., 2020a). In another study, participants with internet gaming disorder again regulated craving for gaming during ROC and emotion regulation tasks, and, under the upregulation and downregulation conditions, transcranial direct current stimulation (tDCS) of the right dorso-lateral prefrontal cortex (dlPFC) was found to increase and decrease craving, respectively (Wu et al., 2020b). A similar pattern was seen in the emotional regulation condition. Supporting the construct validity of the ROC task, Giuliani et al. found that the extent to which individuals downregulated cravings during a food version of the task was linked to other measures of food-related regulation such as the restraint subscale of the three-factor eating questionnaire (Giuliani et al., 2013). Using an ROC task that encouraged downregulation of unhealthy foods and upregulation of healthy foods, Boswell et al. found that healthy participants consumed fewer calories, supporting a role for ROC in modulating eating behaviors (Boswell et al., 2018).

5.2.3. Drug sensitivity of the AAT and ROC—Human research on sensitivity of AAT and ROC tasks to therapeutic intervention is mostly limited to studies employing behavioral rather than pharmacological interventions (Clinicaltrials.gov, 2022c; Mathew et al., 2021) or studies employing tDCS or transcranial magnetic stimulation interventions (Schluter et al., 2018; Wu et al., 2020a). Some intervention studies have used AAT or ROC tasks to drive changes in approach bias or capacity to regulate craving (Sun and Kober, 2020). For pharmacological interventions, the effects of oxytocin manipulation on AAT POMs have been investigated (Alaerts et al., 2021; Schneider et al., 2020; Yao et al., 2018) and one study is examining effects of cannabidiol versus placebo in AUD on outcomes including an alcohol AAT (NCT05387148) (Clinicaltrials.gov, 2022h). Despite a relative lack of data on drug sensitivity, AATs may be valuable in development of drugs posited to have effects on early, fast, and semi-automatic aspects of processing which bias individuals towards approach of addiction-related stimuli. In contrast, ROC tasks may be relevant to pharmacological interventions thought to enhance higher-order cognitive control (e.g., via modulation of dlPFC activity).

5.3. Anxiety and fear

5.3.1. Fear conditioning paradigms—In a typical fear conditioning task, a neutral conditioned stimulus is paired with an aversive unconditioned stimulus so that the previously neutral one becomes aversive (CS+) according to a reinforcement schedule. Generalized fear learning that occurs in response to a non-conditioned neutral stimulus (CS-) can also be measured. The reinforcement schedule of the fear conditioning phase determines whether a paired stimulus is neutral (never paired with a punisher), predictable (always or almost always paired with a punisher), or unpredictable (unreliably paired with a punisher). The

fear conditioning phase is sometimes followed by an extinction phase, in which the CS+ is no longer paired with the previously paired punisher. Reinstatement protocols represent another variation involving unannounced re-exposure of original unconditioned stimulus and re-eliciting fear-related responses after successful extinction learning.

Neuropsychological models posit that fear-related disorders are associated with enhanced fear learning, overgeneralization of fear learning to a CS-, and/or impaired extinction. Fear is linked with highly probable, clearly defined, imminent or certain punishments, whereas anxiety is more closely related to responses of low probability, distal or otherwise uncertain punishments (Bradford et al., 2014). Concerning this difference, specific experimental protocols have been developed to investigate processes relevant to fear versus anxiety (Davis et al., 2010b), social anxiety (Lissek et al., 2008), and intrusions (Wegerer et al., 2013). Orexin modulators have been posited as potential treatments for anxiety and fear-related disorders, and therefore fear-conditioning paradigms may prove to be valuable in testing for potential anxiolytic efficacy and cognitive mechanisms of action.

Based on current preclinical evidence, the fear conditioning phenomena and performance outcomes most reliably associated with orexin modulation are: 1) expression of fear, 2) extinction, and 3) reinstatement. Orexin signaling contributes to consolidation and extinction of aversive memories, with excitatory effector neurons in the amygdala involved in regulation of emotional behavior and fear memory (Sargin, 2019). This was demonstrated by pre-treatment of rats with the SO1RA SB-334867 before conditioning, which impaired fear memory when assessed 24 hours afterwards (Sears et al., 2013). Furthermore, SB-334867 administration immediately after conditioning reduced fear memory, but not when administered 4 hours after conditioning (Flores et al., 2014). This supports the case that OX1R is involved during the acquisition/early-consolidation phase of aversive memories. Also, SB-334867 enhanced fear extinction, and administration of orexin-A impaired this process (Flores et al., 2014). The latter study also showed that rats with poor extinction of cue-induced freezing had a higher percentage of activated orexin neurons in the hypothalamus, suggesting that increased orexin neuronal activation may be associated with impaired ability to overcome traumatic experiences (Sargin, 2019; Sharko et al., 2017).

In another study, Chen et al. showed that systemic administration of the DORA TCS-1102 attenuated acute foot-shock-stress-induced fear responses assessed by freezing and induced anxiolytic effects in a subgroup of rats exhibiting high levels of immobility to a novel non-conditioned context the day after the foot-shock episode. In addition, increases in prepro-orexin mRNA levels were correlated with the amount of time rats spent freezing (Chen et al., 2014). Rats pre-treated with SB-334867 were also shown to display less avoidance from cat odor compared to vehicle-treated rats, but no difference in behavior was observed when another type of stressor based on environmental novelty (elevated-plus maze test) was used (Staples and Cornish, 2014). Finally, there is still limited preclinical evidence that the orexin system may play a role in over-generalization of fear. Viviani et al. found that 3-week treatment with the DORA almorexant attenuated over-generalized contextual fear in rats at 5- and 17-weeks washout, compared with the positive anxiolytic control of sertraline (Viviani et al., 2015).

The consensus of studies has led to the idea that the orexin system is involved in specific forms of stress. For example, Furlong et al. showed that wakefulness, exploration, and conditioned fear elicited c-fos expression in orexin neurons, while restraint stress did not (Furlong et al., 2009). Also, rodent studies have shown that only behavioral or physiological responses to specific acute stressors appear to be mediated by orexin, including foot shock, shock-associated or novel context, short-term forced swimming, food restriction, panic-like states, and social stress (Carrive, 2013; Johnson et al., 2012; Yeoh and Wilkinson, 2014). All of these acute stressors evoke adaptive coping responses, such as escape attempts, non-specific aggression-submission, novelty exploration, or freezing in a shock-associated context (Mahler et al., 2014).

Thus far, no clinical studies have tested the effects of orexin modulators on fear conditioning. Unconditioned stimuli in human fear-conditioning protocols are commonly electrical shocks or other painful or aversive stimuli such as human screams, and POMs are often physiological responses including fear-potentiated startle, skin conductance, heart rate, pupil dilation, or neurological imaging measures. Technical requirements may make these setups unfeasible for some clinical trials, and delivery of pain stimuli may raise ethical issues, especially in vulnerable groups. Subjective response to the CS+ and CS- can be collected as POMs, posing lesser implementation issues, although the relative sensitivity of subjective versus physiological responses is unclear. Fear conditioning tasks can also be long in duration to generate reliable learning or extinction for all stimuli. In addition, some analysis procedures incorporate confirmation that individuals have learned the stimulus associations. This may be important in intervention studies, given that pharmacological enhancement of extinction has been observed only in participants who demonstrated low levels of fear compared to those with high fear at the end of the exposure (Smits et al., 2014; Smits et al., 2013a; Smits et al., 2013b; Telch et al., 2014). However, there are no standardized criteria for this performance-outcome-based exclusion and enforcing such criteria can potentially exclude some endpoints or participants, thereby jeopardizing the generalizability of findings.

Although test-retest coefficients for fear-conditioning paradigms are generally high (Torrents-Rodas et al., 2014), reliability should be ascertained for specific endpoints, time intervals and fear-conditioning-paradigm specifications for which prior data are not always available. Lonsdorf et al. provided detailed information about methodological issues for implementing fear-conditioning paradigms in humans, including task design and analysis considerations (Lonsdorf et al., 2017). Also see Haaker et al. for a more specific focus on reinstatement studies in humans (Haaker et al., 2014).

5.3.2. Other paradigms related to fear and anxiety—Two other paradigms are thought to provide objective measures related to anxiety and fear. These are the cold pressor test and CO_2 challenge. These have already been used in clinical investigations of orexin receptor modulators (cold pressor test: NCT02785406, NCT04234997; CO2 challenge: NCT02593682, Kaufmann et al., NCT02812251, NCT03007693) (Clinicaltrials.gov, 2022a, b, f; Kaufmann et al., 2021; Salvadore et al., 2020). However, as these tests depend primarily on responses to physiological challenges rather than responses based on cognitive processing, they are not considered further in this review.

5.3.3. Appetitive and drug cue extinction—Human paradigms that measure appetitive conditioning, for instance with substances of abuse, are of potential relevance for evaluating the efficacy of orexin receptor antagonists given evidence linking orexin modulation with cue-based learning (Cole et al., 2020; Cole et al., 2015; Keefer et al., 2016; Pantazis et al., 2021; Sharko et al., 2017) and the potential of orexin receptor modulators to treat conditions such as SUDs and eating disorders (Han et al., 2020; Steffen et al., 2006; Zarrabian et al., 2020). Appetitive and drug cue associations have been under-researched (Konova and Goldstein, 2019) and nobody has yet evaluated the effects of orexin modulation on appetitive, non-fear domains of extinction in humans. Nevertheless, preclinical work has suggested some similarities between fear and non-fear extinction (Millan et al., 2011; Peters et al., 2009). Additional grounding studies are warranted exploring non-fear extinction in SUDs, eating disorders, gambling disorder, and other conditions characterized by compulsive choice.

5.4. Emotional processing – negative and positive emotional biases

Several paradigms have been developed to measure processing of emotional information. For behavioral measures, processing of emotional stimuli can take different forms, including accuracy in classifying stimuli as positive or negative, speed of categorization, memory for stimuli, or spatial-attentional biases towards emotionally-valenced stimuli. These tasks have been shown to provide measures of emotional processing biases present in mood disorders like depression. Furthermore, many antidepressant compounds reduce processing of negative stimuli and/or enhance processing of positive stimuli. An example of the former would be decreased recall of negative self-referential words, and that of the latter is increased accuracy in identifying happy facial expressions.

Reduced orexin system function has been identified in association with depressive-like behavior in rats with hormonal and behavioral features similar to those observed in patients with depression (Sargin, 2019), and in socially defeated rats that display increased immobility in the forced swim test (Lutter et al., 2008). In adult male diurnal Nile grass rats, LH orexin immunoreactivity was attenuated in a model of seasonal affective disorder using dim light conditions (Deats et al., 2014). Chronically restrained mice that show multiple measures of depressive-like behavior had increased orexin mRNA levels in the amygdala and knocking down orexin expression reversed these behaviors (Kim et al., 2015). OX1R knockout mice showed decreased immobility time in a forced swim test study, an indication of reduced “depressive-like” behavior (Abbas et al., 2015). Also, pharmacological blockade with the DORA almorexant during unpredictable chronic mild stress decreased subsequent immobility in the tail-suspension test as an indication of antidepressant-like effects similar to the serotonin specific reuptake inhibitor fluoxetine, and restoration of the associated stress-induced HPA axis impairment (Nollet et al., 2012).

As orexin receptor modulators are posited to have a role in ameliorating symptoms of depression and anxiety, we focus here on the emotion-processing POMs which have been used the most in experimental medicine studies of antidepressant and anxiolytic compounds. These are tasks of facial expression recognition, emotional categorization, recall and recognition, and dot-probe tasks (Table 1). Several studies have suggested that emotion-

processing patterns deviate significantly in patients with psychiatric disorders compared to healthy controls. MDD is the most intensively studied and has consistently been associated with increased processing of negative versus positive emotional information (Panchal et al., 2019; Warren et al., 2015). In anxiety studies, the findings have not been consistent. For example, some studies using recognition of facial expressions have shown that highly anxious individuals are more sensitive than healthy individuals to fearful or threatening faces, and more likely to interpret neutral or ambiguous faces as threatening (Bell et al., 2011; Doty et al., 2013; Gutiérrez-García and Calvo, 2017; Heuer et al., 2010; Richards et al., 2002; Surcinelli et al., 2006). Others reported either no case-control differences (Cooper et al., 2008; Jusyte and Schonenberg, 2014; Philippot and Douilliez, 2005) or reduced sensitivity to negative facial expression in anxiety (Jarros et al., 2012; Montagne et al., 2006). Some of the heterogeneity may be driven by variability in the study populations and paradigms used, and/or inconsistencies in measuring anxiety state versus anxiety trait.

There have been no meta-analyses of emotion-processing patterns in SUDs, eating disorders, or other conditions of compulsive or addictive behaviors. However, difficulties recognizing disgust and tendencies to interpret non-angry faces as angry ones in bulimia nervosa have been observed (Dapelo et al., 2017), suggesting nuanced aberrancies in processing negative emotional information. In another study, people with binge drinking showed impairments in recognizing all expressions compared to healthy individuals, and extent of impairment was related to alcohol consumption (Lannoy et al., 2018). These findings suggest that general cognitive or emotional difficulties are associated with binge drinking, rather than specific difficulties in processing negative versus positive information.

The dot-probe task has conceptual roots in neuropsychological models of anxiety, measuring attention and orientation to negative or threatening information. While socially anxious individuals preferentially allocate attention towards threatening faces, a meta-analysis of dot-probe studies in anxiety found heterogenous results, suggesting that measuring this bias may depend on type and duration of reference stimulus, and clinical level of social anxiety (Bantin et al., 2016).

Dot-probe results in studies of eating disorders have also been equivocal. A version of this task which employed disease-relevant food stimuli did not differentiate between healthy individuals and those with either bulimia nervosa or BED (Leslie et al., 2019). Furthermore, Svaldi et al. reported that adults with obesity with or without BED showed similar levels of food-stimuli cueing in a task similar to the dot-probe (Svaldi et al., 2015). However, using a spatial cueing paradigm similar to the dot-probe, Schmitz et al. found that patients with BED showed more priming to food compared to weight-matched healthy individuals, which correlated with reported severity of binge-eating symptoms (Schmitz et al., 2014). Thus, the validity of the dot-probe task to measure clinically relevant aspects of cognitive dysfunction in eating disorders is unclear.

Evidence in the field of SUDs and other compulsive behaviors may be more informative. Lubman et al. used a pictorial dot-probe task to investigate attentional biases to stimuli associated with drug use in opioid use disorder. Participants with this disorder had faster reaction times to probes that replaced drug pictures rather than neutral pictures,

consistent with an attentional bias to drug-related stimuli (Lubman et al., 2000). Along the same lines, Townshend et al. found that individuals with heavy but non-dependent social drinking showed attentional biases towards alcohol-related stimuli compared with those with occasional social drinking in a dot-probe task that employed alcohol-related pictures and words as primes (Townshend and Duka, 2001). Attentional biases to sexual cues during performance of a dot-probe task have also been reported in men with compulsive sexual behaviors (Mechelmans et al., 2014).

Tasks of emotional processing are sensitive to antidepressant compounds, in healthy volunteers and participants with depression (Warren et al., 2015). This is based on data collected in tasks of facial expression recognition, emotional categorization, and emotional recall. However, few studies have investigated aspects of task validity, such as test-retest reliability. Adams et al. found no effect of repeat testing in healthy controls on emotional word categorization, recall or recognition, with limited effects of repeated testing on facial expression recognition one week after baseline. Although performance outcomes in a facial expression recognition test (FERT) was better after one week compared to baseline, there was no effect of repeat testing on relative accuracy for specific emotions (Adams et al., 2016). Furthermore, Thomas et al. reported no effect of session number on performance outcomes in healthy individuals in an emotional categorization task and found that practice effects had stabilized after two sessions for facial expression recognition, emotional word recall, and emotional word recognition tasks (Thomas et al., 2016).

See Table 1 for details of implementation issues and considerations for each of the emotional processing tasks considered above.

5.5. Response inhibition

Response inhibition refers to withholding of actions that are inappropriate in certain contexts and deleterious to goal-directed behavior. Tasks of response inhibition involve control of attention, behavior, thoughts, and/or emotions to override predispositions or contextual lures (Diamond, 2013). Decreased response inhibition is associated with impulsivity which, in turn, is associated with clinical indications linked to the orexin system, including SUDs and eating disorders, characterized by problematic behavioral patterns (Hamilton et al., 2015b; Moeller et al., 2001). In line with this, recent preclinical studies have found that increased activation of medial hypothalamic orexin neurons was correlated with higher accuracy in a palatable-food go/no-go (GNG) task (Freeman and Aston-Jones, 2020), while suvorexant reduced cocaine-induced premature responding in the 5-choice serial reaction time task that assesses response impulsivity (Gentile et al., 2018b).

Several experimental medicine tasks provide measures of response inhibition in humans. Here we focus on the GNG, stop signal (SS), and Stroop tasks, as these are technically less challenging to implement and can easily incorporate affective or disease-relevant stimuli (Table 2). The basic framework of the GNG and SS tasks can be employed in both preclinical and clinical research. The GNG task has shown cross-species consistency in studies on neurobiological underpinnings of impulsivity and effects of drug manipulation (Eagle et al., 2008; Hamilton et al., 2015a). For example, rat studies have implicated serotonin as a modulator of impulsivity (Harrison et al., 1999), whilst in human research

fMRI effects during no-go (response inhibition) trials are differentially affected by administration of citalopram vs. tryptophan depletion (interventions posited to increase and decrease serotonin activity, respectively) (Macoveanu et al., 2013). The SS task has also shown some cross-species consistency in neural circuitry. For example, noradrenaline reuptake inhibitors improve SS task performance in both humans and animals (Chamberlain et al., 2006; Robinson et al., 2008). Similar brain areas have been implicated across species, with rat-lesion models and fMRI studies suggesting prefrontal cortical involvement in SS task performance (Aron et al., 2007; Bari et al., 2011).

Response inhibition tasks were designed to gauge rapid response impulsivity as specific measures of response inhibition subtypes (Fineberg et al., 2014; Hamilton et al., 2015b). Schachar et al. suggested that the GNG task provides a measure of action restraint (preventing action before initiation) while the SS task assesses action cancellation (inhibiting response during execution) (Schachar et al., 2007). This distinction is supported by a meta-analysis of fMRI results revealing distinctions in the neural networks recruited by GNG and SS tasks (Swick et al., 2011). This has led to recommendations that researchers consider using both tasks for assessments of response inhibition (Hamilton et al., 2015a). For many clinical trials, this may be limited by participant burden. It may also be important to determine if specific aspects of response impulsivity are aberrant in the population under study and/or have an established association with clinically relevant measures before initiating clinical testing.

The basic Stroop and emotional Stroop tests assess response inhibition and attentional biases, such as orienting towards and/or avoidance of stimuli, as well as cognitive conflict and interference impulsivity. Therefore, Stroop tasks may be considered not to be specific measures of response inhibition, but rather of assessing cognitive control (Bustamante et al., 2021; Starzomska, 2017).

The classical GNG, SS, and Stroop tasks have been adapted to include affective or disease-relevant stimuli to increase ecological validity and sensitivity in specific clinical populations. Some researchers have speculated that disease- or symptom-specific stimuli may be important to isolate distinct differences that contribute to the emergence and maintenance of psychiatric problems. One example of this is the use of food-related stimuli in eating-disorder populations (Berner et al., 2017). Limited systematic research comparing disease-relevant and neutral stimuli in response-inhibition tasks has suggested greater impairments in inhibitory control when disease-relevant stimuli are used in some groups (Wu et al., 2013). On the other hand, a study by Lyu et al. found no difference in false alarm rate (response inhibition) when comparing women who binge eat and weight-matched individuals without binge eating, when performing a GNG task incorporating food (disease-relevant) stimuli and household object (neutral) stimuli (Lyu et al., 2017). We suggest that, where possible, both disease-relevant and neutral stimuli should be used to determine specific versus generalized effects of orexin receptor modulation.

A meta-analysis of GNG- and SS-related POMs in patients with heavy substance use or addiction-like behaviors found significant case-control differences for heavy use/addiction to cocaine, tobacco, and alcohol and gambling (Smith et al., 2014). A meta-analysis

of the emotional Stroop task found that individuals with post-traumatic stress disorder (PTSD), MDD and anxiety disorders showed greater interference by disease-related stimuli, compared with healthy individuals (Joyal et al., 2019). Furthermore, people with PTSD and affective disorders showed more interference from positive and negative stimuli, respectively. Wu et al. conducted a meta-analysis of neuropsychological studies on inhibitory control in bulimic-type eating disorders, considering both general and disease-specific stimuli. This included studies using the GNG, SS, and Stroop tasks, which identified significant deficits in response inhibition across bulimic-type eating-disorder groups for general stimuli and greater impairments in inhibitory control in bulimia nervosa for disease-relevant stimuli (Wu et al., 2013). However, a recent meta-analysis by Cury et al. found impaired working memory in individuals with obesity and BED in comparison to those with obesity without BED (Cury et al., 2020).

Some studies have reported drug sensitivities of response inhibition tasks. In a randomized controlled trial of treatment-resistant depression, in which patients received 0.5 mg/kg ketamine, 0.2 mg/kg ketamine or saline infusion, Chen et al. found an increase in GNG correct responses and a decrease in omission rate in the high-dose ketamine group at day 14 post-infusion. Also, the improvement in sustained attention and response control was negatively associated with depressive symptoms in the high-dose ketamine group, suggesting improved cognitive function (Chen et al., 2018). Nathan et al. examined effects of the GSK598809 dopamine D3 receptor antagonist versus placebo on attentional bias to rewarding food cues in individuals with overweight and obesity and binge and emotional eating. In a Stroop task with food stimuli, the GSK598809 treatment had no effects on attentional bias, although bias scores were inversely correlated with a measure of eating restraint and allowed identification of low- and high-restraint subpopulations (Nathan et al., 2012). Pringle et al. assessed the effects of acute low-dose acute tryptophan depletion (ATD) in females who were dieting. While ATD had no significant effect on mood or hunger, it led to increased interference during the processing of negative stimuli in a masked version of the emotional Stroop test, including stimuli related to eating, weight, and shape (Pringle et al., 2012). As another example of drug sensitivity, Franken et al. found that after a single oral dose of haloperidol versus placebo, detoxified heroin-dependent patients' performance outcome was better in an emotional Stroop task, which included heroin-related or neutral words (Franken et al., 2004).

Other studies have reported the ecological validity of response inhibition tasks, modified to involve presentation of disease-specific stimuli. For example, individuals with obesity and BED made more errors in a food- and body-specific version of the GNG, compared to individuals with obesity alone (Mobbs et al., 2011). Decreased response inhibition in a food GNG correlated with trait-like attentional impulsiveness in BED (Hege et al., 2015), helping validate the GNG as a measure of impulsivity in this population. Another study found alcohol-specific impairments in response inhibition in individuals with binge drinking (Czapla et al., 2015). The same study showed that false alarms to alcohol stimuli were a significant predictor of binge drinking, and this had greater predictive power than general impulsivity scales. These findings support the sensitivity of disease-specific GNG tasks in identifying disease-relevant impulsivity differences.

The response inhibition tasks described above are often associated with few implementation complexities, although sourcing and selection of image stimuli may be subject to the same issues as described for the AAT and ROC (see previous section). Table 2 also provides more detail about implementation issues for each of the response inhibition tasks considered here.

6. Limitations and challenges

This review supports the proposition that experimental medicine approaches can be valuable in at least two aspects of drug development: 1) translation of preclinical findings to relevance in humans, and 2) characterization of the effects of treatments in clinical trials. However, there are still limitations and challenges for each of these applications.

6.1. Translating research from animals to humans for drug development: POMs considerations

The ‘fail-fast’ approach is predicated on the goal of eliminating early candidate drugs that are unlikely to be successful. We posit that experimental medicine approaches could bridge the translational gap of limited predictive utility of animal models in psychiatry, given the subjective nature and heterogeneity of many psychiatric disorders. The methods used to assess target engagement and treatment effects should be founded on sound understanding of the fundamental biology and pathology of the disorder in question (Gould and Manji, 2004). Unfortunately, knowledge of underlying molecular factors contributing to disease and mechanisms remains inadequate and has not materialized into new and efficacious treatments for psychiatric disorders, compared to other disease areas. While some of the POMs described above could be linked to dysregulation of various neurotransmitter systems, use of these measures can lead to wrong conclusions about drug effects if knowledge is not available regarding how and when a specific behavioral change impacts the disease. There is also the requirement of knowing how these POMs signal dysregulation of the orexin system. In addition, disease heterogeneity may impact the interpretation of these outcomes, as may also be the case with clinician- and patient-reported outcomes. Evaluation within clearly defined patient and control groups may constitute a critical first step to establishing assay sensitivity, independent of intervention effects. Thus, variables such as age, sex/gender, disease presentation, medical history, cultural diversity, and genetic background should be considered when designing these studies. Other important challenges include demonstrating reproducibility of findings and taking into account standardized implementation of the POMs and appropriate statistical analyses. The potential advantage of trans-diagnostic relevance of some of these POMs may need to be balanced against the targeting of more pronounced manifestations of an outcome of interest, when researching a specific condition.

6.2. Characterization of treatment effects and clinical benefit

A key challenge to wider use and acceptance of POMs to support drug development and eventual approval is the lack of formal scientific guidance. Despite the current lack of specific guidance on evidentiary requirements for POMs in drug development and registration, many of the principles described in the FDA Patient-Reported Outcome guidance are applicable, including endpoint modeling, choice of instrument, content validity, test-retest reliability, ability to detect change, ceiling/floor effects, other psychometric

properties, clinical trial design, and data analysis (U. S. Food & Drug Administration, 2009). Since COAs are intended to measure treatment effects on how a patient feels or functions, it should be clear what aspect of the condition the POM represents. Hence, the concept of interest and context of use in which the measure is applied are critical to the choice of paradigm and corresponding assessment. A consistent understanding of assessment instructions by trial subjects and investigators and unambiguous interpretation of scores are further elements of content validity that should be demonstrable in association with the behavioral outcome. In addition, it should be determined if the results obtained with POMs stand alone or if additional data from other COAs are needed to interpret the findings.

Establishment of clinically meaningful within-patient change is another important aspect of COA development and validation and may challenge POMs. For example, depressed patients often do not respond to the first antidepressant prescribed, resulting in multiple attempts to find a treatment at a suitable dose that reduces symptoms. As a result, for some patients it can take months before symptoms are reduced. A personalized medicine approach offers a means of reducing this delay by utilizing early biomarkers of treatment response. Browning et al. assessed the clinical effectiveness of such an approach using a predictive algorithm based on the FERT combined with measures of subjective symptoms to guide antidepressant treatment (Browning et al., 2019). They conducted a multi-center, open-label, randomized controlled trial with 913 medication-free depressed patients assigned to have their antidepressant treatment guided by the predictive algorithm (PReDicT arm) or treatment as usual. There was a significantly greater reduction in anxiety symptoms at week 8 and a greater improvement in functional outcome at week 24 in the PReDicT arm, showing that POMs can also be deployed to improve real-world outcomes.

Normative data for disorders with many phenotypes may not exist or otherwise be difficult to generate. Relevance to patient day-to-day activities is often used to gauge clinical meaningfulness, and the behavioral concepts assessed by POMs may not be linked directly to these or may be associated with other activities that are difficult to disentangle. There are also operational challenges that come with implementation of POMs across different age groups and in global clinical trials with culturally diverse populations. Cognitive behavior is influenced by environmental and socio-economic factors, and ensuring consistency in implementation and interpretation of POMs needs to go beyond simple language barriers to cross-cultural adaptation. Finally, feasibility of implementation also depends on complexity, duration and frequency of the task/assessment, and may involve complex considerations for some psychiatric conditions.

7. Conclusions and future perspectives

There remains an unmet medical need in the treatment of neuropsychiatric disorders. Despite progress in understanding the biological underpinnings of these disorders, translation of basic neuroscience findings to development of novel and improved therapies has been slow to materialize. In this review, we have described how experimental medicine approaches can identify POMs to provide an indication of efficacy throughout the drug development process, using modulators of the orexin system as an example. Preclinical studies have implicated the orexin system in emotional, cognitive, and behavioral processes,

including stress responses, reward processing, motivations, feeding, and sleep. The first clinical investigations of orexin receptor antagonists in psychiatric disorders, besides insomnia, have started, and some initial promising results in the fields of MDD and SUDs have emerged. The investigation of the effects of orexin receptor agonists in the clinic is still in its infancy and may hold great promise for the future.

Use of POMs may facilitate research on the orexin system and other targets in the field of psychiatry by providing more objective measures of brain function, complementing the standard patient-reported or clinician-observed changes in symptoms. While there are still challenges surrounding the development, validation, and operationalization of these POMs arising from experimental medicine approaches, we encourage the inclusion of these measures in studies investigating the effects of novel drugs for neuropsychiatric disorders. Since these assessments are intended to measure treatment effects at the symptom level, the concept of interest and context of use are important in the choice of paradigms and corresponding POMs. This requires understanding of assessment instructions by study participants and investigators, and unambiguous interpretation of assessment scores, depending on the types of behavioral outcomes being assessed.

Wider use and acceptability of POMs generated by experimental-medicine approaches will benefit from collaborative partnership models. Public-private partnerships (PPPs) such as NIMH-MATRICS and the EU's Innovative Medicines Initiative (https://www.imi.europa.eu/) can offer an arena for cooperation between diverse stakeholders including not only pharmaceutical companies and Universities, but also small- and medium-sized enterprises (SMEs), regulatory bodies, health-technology-assessment organizations and patient groups (de Vrueh et al., 2019).

PPPs are seen as well-suited to pre-competitive research initiatives (de Vrueh and Crommelin, 2017) such as those that working towards the validation of POMs. PPPs in the area of CNS research have in some cases demonstrated impact in, for example, the form of tools, standards, platforms, and cohort datasets (de Vrueh and Crommelin, 2017; Innovative medicines initiative, 2016; O'Rourke et al., 2022). However, translation of research into tangible benefits that meet industry partner needs, sustainability, administrative burden, and management of non-performing partners can be issues of concern (O'Rourke et al., 2022). Furthermore, the timelines associated with PPPs – often playing out over the course of 5 or more years, not including application timelines – can be at odds with the more rapid pace of change in the objectives of industry partners. The IMI-funded PRISM project initially included seven pharmaceutical partners (https://prism-project.eu/en/prism-study/), whilst the follow-on PRISM2 project has only one (https://prism-project.eu/en/prism-study/), possibly reflecting change in business objectives of these companies over the projects' lifetime. An alternative model for collaborative partnership which can offer more agility is the SME-led private precompetitive consortia, such the Reward Task Optimization consortium (https://www.p1vital.com/research/rtoc/). Although associated with different strengths and weaknesses, these different frameworks represent important opportunities for technical validation of experimental-medicine approaches for research or drug-registration purposes, and also adoption of such approaches in real-world clinical practice.

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Highlights

- Translation from animal models to clinical use in psychiatry remains challenging
- Experimental medicine approaches may support investigation of efficacy in humans
- Preclinical studies suggest potential of orexin modulation in psychiatric disorders
- Experimental medicine approaches in studies of orexin modulation are reviewed
- Validation and operationalization are key challenges to more widespread adoption

Box 1.

Advantages of POMs

Potential advantages of POMs arising from cognitive/behavioral tasks over other outcome measures typically used in clinical trials in psychiatry include:

- An objective indication of brain function and behavior
- Reduced sensitivity to reporting biases and placebo effects
  - Keefe et al., for example, found minimal placebo effects on performance-outcome using a cognitive test battery in a study of patients with schizophrenia (Keefe et al., 2017)
- Providing a cognitive/behavioral signature similar to a molecular or imaging biomarker as an objective measure of biological state (particularly useful in the translation from preclinical to clinical research)
- Mostly devoid of the expense and technical challenge of assessing neural activity directly through techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography, or electroencephalography (EEG)

Box 2.

Key questions when using experimental medicine approaches with cognitive POMs in intervention studies

- Which domains of cognition or perception are thought to be affected by the intervention, based on prior preclinical or clinical evidence?
- If preclinical data exist, do the animal models have human analogues for use in clinical studies?
- What is known about the target indication(s) and are the same domains of cognition known to be impaired in the patient population being studied?
- Is there evidence that impairment is linked to severity of illness or outcomes in the population?
- Is there evidence of test-retest reliability using the performance outcomes of interest?
- Do previous results show consistency, replicability, and drug effects for shortlisted paradigms?
- Are there potential implementation concerns such as technological requirements?
- Are there substantial data management or analysis challenges to be overcome?
- Are there potential language or cultural considerations and, if so, are there data to indicate the magnitude of these effects?

Box 3.

Reward processing tasks and participant reimbursement in clinical trials

- In some studies, participants are given actual rewards for their performance rather than merely hypothetical rewards.
- Regarding ITCTs, Hamilton et al. reported that use of hypothetical rewards and real rewards results in equivalent performance outcomes (Hamilton et al., 2015c).
- Such effects may vary across reward processing tasks and clinical populations.
- For monetary rewards, the practicalities of reimbursement should consider standardization across different currencies and geographical locations, reflecting purchasing power parity.

Box 4.

Implementation issues for the AAT and ROC tasks

Sourcing and selection of image stimuli

- Stimulus categories like disease-relevant and neutral images should be matched on characteristics such as size, brightness, and contrast.
- Cross-cultural applicability of images should be considered in international clinical trials.
- Existing databases of affective images offer pictures standardized for image quality metrics and provide normative data across cultures (e.g., the Cross Cultural Food Image Database) (Toet et al., 2019).
- Available information varies in different image libraries.
- Some images are currently unavailable for use in commercial research.

Fatigue related to task duration

- AATs typically take 20 minutes to complete, including practice trials (Rinck and Becker, 2007).
- ROC tasks require participants to complete a cognitive reappraisal training session before the assessment task itself, which together have a duration of approximately 20–25 minutes.

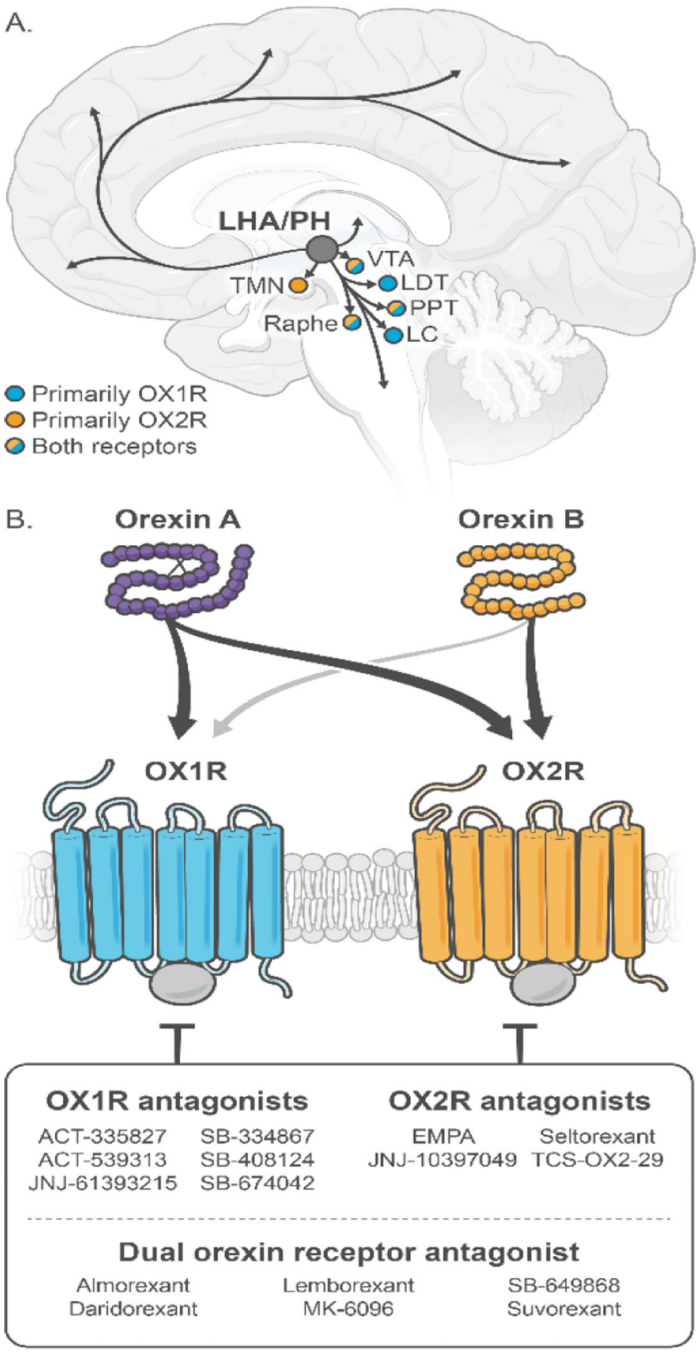

Figure 1.

(A) The orexin system in the human brain, with differential distribution of OX1Rs (blue) and OXR2s (orange) depicted. (B) The two orexin peptides (Orexin A and Orexin B), orexin receptors, and antagonists. OX1R, type 1 orexin receptor; OX2R, type 2 orexin receptor. Abbreviations: LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; LHA, lateral hypothalamus; OX1R, orexin type 1 receptor; OX2R, orexin type 2 receptor; PH, posterior hypothalamus; PPT, pedunculopontine nucleus; TMN, tuberomammillary nucleus; VTA, ventral tegmental area.

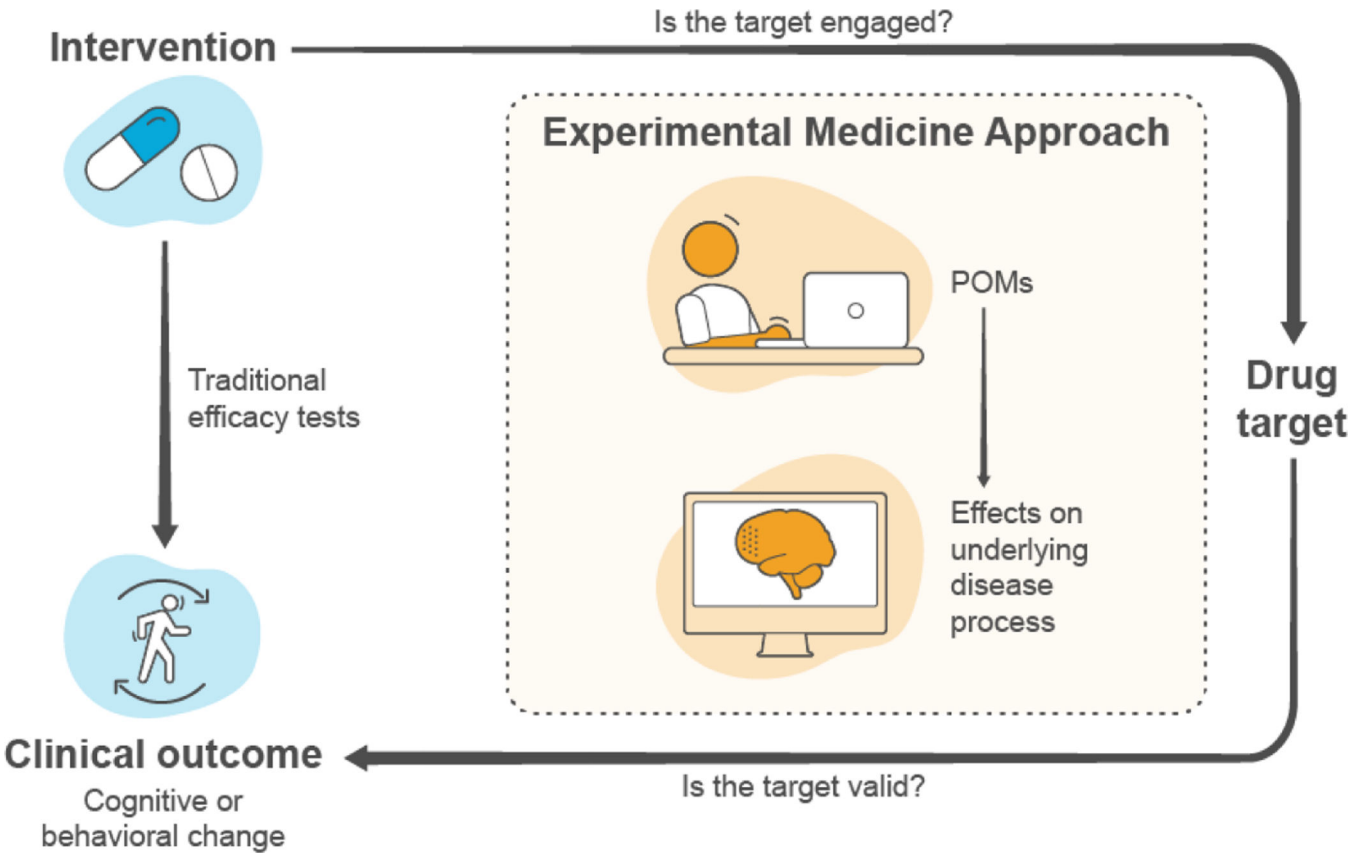

Figure 2.
Schematic of the experimental medicine approach to drug development.

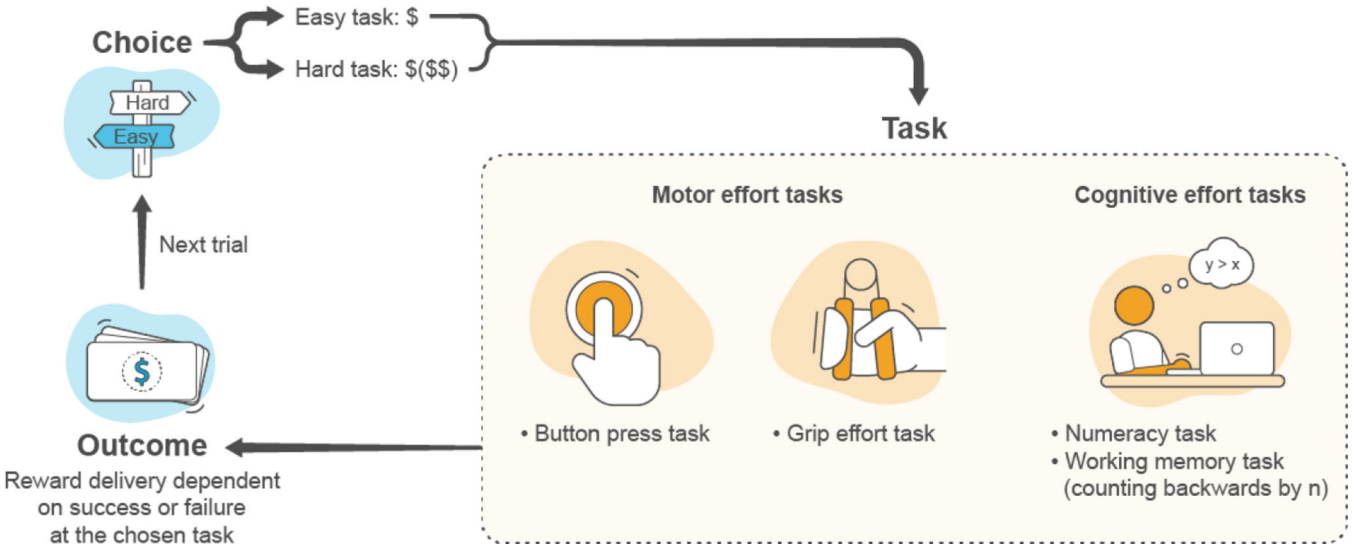

Figure 3.

Basic trial structure of effort-based decision-making tasks. Participants choose between completing an easier task or a harder task, which may be associated with different magnitudes of reward or expected value. The participant then attempts to complete their chosen task. The kind of effort that the participant must make depends on task structure, but can e.g. be a form of motor effort or cognitive effort. Trial outcome, i.e. reward delivery, depends on whether the participant completes the task or not. The participant completes a series of trials from which indices can be extracted providing a measure of willingness to expend effort for rewards.

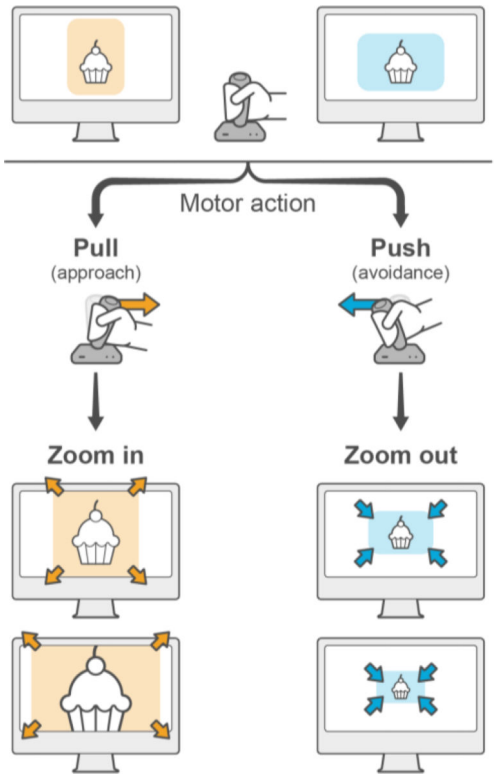

Figure 4.

Basic trial structure of the Approach Avoidance Task. Participants are presented with an image which they must respond to with a motor action that simulates approach (e.g. pulling a joystick) or avoidance (e.g. pushing a joystick). The task is a measure of 'implicit' approach and avoidance, not explicit approach and avoidance. Participants are instructed to execute the action ("push" or "pull") depending on an image property such as it being presented in landscape or portrait orientation, and not dependent on image content. In the example depicted, participants are instructed to pull the joystick for images in portrait orientation, and push the joystick for images in landscape orientation. Images increase in size (zoom in) or decrease in size (zoom out) in response to a "pull" or "push" action, respectively, to further simulate approach and avoidance. Approach bias values are calculated based on median reaction time differences between "push" and "pull" trials.

Table 1.

Experimental medicine tasks that provide measures of emotional processing in humans

Task and aspect of emotional processing measured	Task description	Key performance outcome(s)	Potential implementation and analytics issues
Facial Expression Recognition Tasks Measuring perception / identification of affective information (facial emotional expression)	On each trial participants are presented with an image of a face showing a facial expression and must indicate the expression shown.	Accuracy, reaction time, misclassifications, target sensitivity, and response bias, by category of facial expression.	Many versions of the task exist, and it is unclear to what extent previous findings generalize across task version. Cognitive demand of task is modest, although some longer task designs can potentially lead to fatigue. Cross-cultural validity and standardization is a consideration for facial expression image libraries, given observations that accuracy for emotion recognition is higher for faces from member of the same cultural group (Elfenbein and Ambady, 2003) in a way that may interact with effects of diagnosis (Hunter et al., 2009; Kang et al., 2019). Task can yield a relatively high number of POMs, leading to potential multiple comparison issues at statistical analysis. There is little consistency in the literature regarding the precise endpoints that show case-control or drug effects; this may depend on population and drug mechanism of action.
Emotional Categorization Tasks Measuring speed of processing of affective information	On each trial participants are presented with a stimulus (e.g. a personality characteristic word such as “hostile” or “honest”) and asked to categorize it as positive or negative.	Reaction time to correctly classifying positive vs. negative stimuli. Less commonly, accuracy for positive / negative stimuli, and frequency of classifying stimuli as positive / negative.	Stimuli need to be standardized across cultures / languages. Note, emotional categorization tasks can be viewed as a necessary precursor to tasks of emotional memory and emotional recall (see following two rows). Duration of these individual is typically relatively short (in the range of 5–10 minutes); however, the combined duration of the series of tasks may result in fatigue in some study designs and populations.
Emotional Recall Tasks Measuring free-recall memory for affective information	Participants are asked to freely recall (e.g. writing or typing) as many positive and negative stimuli as possible, previously presented in e.g. an emotional categorization task.	Number of stimuli (e.g. words) correctly recalled, for positive and negative stimuli.	Some versions of the task implement a “surprise” free recall procedure, and for repeated-measures study designs, the surprise element may be necessarily lost. See also implementation issues associated with Emotional Categorization Tasks (above).
Emotional Recognition Memory Tasks Measuring recognition memory for affective information	On each trial participants are presented with either a stimulus that was previously presented to them (for example in an emotional categorization task), or a previously unseen (novel) stimuli. For each stimulus, participants are required to indicate whether it was previously presented.	Number of stimuli correctly identified as previously presented; errors of omission; false alarms (errors of commission); target sensitivity; and response bias; for positive and negative stimuli.	See implementation issues associated with Emotional Categorization Tasks (above).
Dot Probe Task Attention to, or spatial orientation to, affective information	On each trial participants are presented with two stimuli on the computer screen, which are replaced by a target pair of dots in the spatial location of one of the initially presented stimuli. The participant responds by indicating whether the dots are vertically or horizontally aligned. Typically there is a manipulation between the two stimuli that were initially presented. For example, one may be disease-relevant (e.g., a fearful face) and the other may be a control stimulus (e.g., a happy or neutral face). The reaction time to respond to the	Difference in reaction time to target, when target is in the same spatial location as the disease-relevant stimuli vs. control stimuli.	May require specialized hardware, because of high temporal precision required for delivering stimuli (including, in some task designs, masking stimuli) and recording responses. Task duration typically 5–10 minutes.

Task and aspect of emotional processing measured	Task description	Key performance outcome(s)	Potential implementation and analytics issues
	dots can be used as a measure of attention to the disease-relevant vs. control stimuli. Experimental stimuli can be masked or unmasked (allowing the assessment of very fast, automatic orienting/attention to masked emotional stimuli).		

Table 2.

Experimental medicine tasks that provide measures of response inhibition in humans

Task	Task description	Key performance outcomes	Potential implementation and analytics issues
Go/No-Go task / Affective Go/No-Go task *	In the classic Go/No-Go task the participant must respond rapidly to a cue (e.g., X) but withhold a response when a no-go stimuli is shown (e.g., O). Typically target stimuli are presented more frequently than non-target stimuli (e.g., at a ratio of 3:1) in order to elicit prepotent responses to the target stimuli. Go/No-Go tasks that include affective or disease-relevant stimuli have been developed (Hege et al., 2015; Lyu et al., 2017; Mobbs et al., 2011). False alarms are the key performance outcome associated with response inhibition. Other measures include errors of omission, hits, successfully inhibited responses, and reaction times for hits. Some researchers calculate target sensitivity and/or response bias, although these appear to be less favored in the literature (Meule, 2017), possibly because interpretation is more unclear. Where different conditions have been employed, endpoints are explored by task condition, e.g. false alarms to affective stimuli vs. false alarms to neutral stimuli. Task is often quite long (approximately 15 minutes) to allow for a sufficient number of false alarms (Hege et al., 2015; Lyu et al., 2017). If adopting an affective version of the Go/No-Go, affective stimuli can be paired with the Go or the No-Go response, or both, and the task can take a block design or a mixed trials design. Block designs can allow investigation of the participants' ability to shift between rules (Meule, 2017). However, this can extend task duration and increase participant burden. Stop Signal Reaction Time task / Affective Stop Signal Reaction Time Task * Participants	False alarms are the key performance outcome associated with response inhibition. Other measures include errors of omission, hits, successfully inhibited responses, and reaction times for hits. Some researchers calculate target sensitivity and/or response bias, although these appear to be less favored in the literature (Meule, 2017), possibly because interpretation is more unclear. Where different conditions have been employed, endpoints are explored by task condition, e.g. false alarms to affective stimuli vs. false alarms to neutral stimuli.	Task is often quite long (approximately 15 minutes) to allow for a sufficient number of false alarms (Hege et al., 2015; Lyu et al., 2017). If adopting an affective version of the Go/No-Go, affective stimuli can be paired with the Go or the No-Go response, or both, and the task can take a block design or a mixed trials design. Block designs can allow investigation of the participants' ability to shift between rules (Meule, 2017). However, this can extend task duration and increase participant burden.
Stop Signal Reaction Time task / Affective Stop Signal Reaction Time Task *	Participants perform a continuous or repetitive motor response, for example repeatedly pressing a button or touching a screen, in response to a 'go' cue. On some trials the 'go' cue is proceeded by a 'stop' cue indicating that the participant should withhold the response. The task can be modified to include affective stimuli, for example by presenting affective images prior to the go cue (Kalanthroff et al., 2013) or using affective stimuli as the go or stop cues (Svaldi et al., 2014).	Stop signal reaction time (SSRT), which is a measure of the speed of inhibiting the response after the stop cue has been given. Since correct inhibitions result in a lack of response the SSRT cannot be directly measured, and therefore mathematical models such as the independent race model (Logan and Cowan, 1984) are used to estimate the SSRT based on other endpoints such as the RT on unsuccessful stop trials, RTs on go trials, and the probability of making a false response.	There can be challenges when estimating the SSRT. Researchers must ensure that task design is appropriate for the given population, generating sufficient number of both successful and unsuccessful stop trials. Analysts must ensure that the underlying assumptions of the mathematical model are met before estimating the SSRT, otherwise estimates and therefore conclusions may be unreliable. See Verbruggen et al. for a comprehensive review of challenges in the design and analysis of the Stop Signal Task (Verbruggen et al., 2019). Task duration is approximately 10 minutes.
Stroop / Emotional Stroop *	Participants must respond to one feature of presented word stimuli, which is incongruent, on some trials, with the semantic properties of the word presented. For example the word 'blue' is presented in red color font, and the participant must name the color and inhibit the prepotent response to read the word. In the affective version of the Stroop, and those based on substances of abuse, disease-relevant word stimuli may produce attentional biases towards or away from the stimuli, compared to neutral word stimuli.	Accuracy and reaction time (for correct responses) for each trial type (e.g., incongruent vs congruent stimuli, or diseaserelevant vs. neutral).	As with the Affective Go/No-Go task, the Emotional Stroop can be implemented in either a block design or a mixed design. Stroop tasks are usually implemented with either button-press responses or vocal responses. However, we are not aware of comparative research which compares and contrasts these response types. Finally, there is a choice of whether or not to use masked stimuli. Duration of task incorporating several stimulus categories is roughly 5–10 minutes.

* If using image stimuli, there are considerations to be made about sourcing and selecting images (see main text).