Abstract
Anhedonia is defined as reduced interest or pleasure in activities previously considered enjoyable and is a cardinal symptom of many neuropsychiatric disorders including major depression, schizophrenia and substance dependence. Pleasurable experiences involve a variety of psychobiological components including learning, memory and motivation that influence engagement with rewarding events and can therefore impact affective responding. Despite the capacity to dissociate these processes in humans and nonhuman animals, contemporary preclinical animal models of anhedonia emphasize responses to immediately pleasurable stimuli including palatable food and drugs of abuse. This limits translatability to the clinic as human patients exhibiting anhedonia largely display normalized responsivity to pleasurable stimuli and instead show deficits in responding for associative cues. Conditioned motivators can serve to bridge the gap between clinical and preclinical knowledge, as they can be dissociated into each independent component process associated with anhedonia. Following several distinct temporally-contingent pairings, such as palatable food, drugs of abuse, sex, and sociability, conditioned motivators can serve to bridge the gap between clinical and preclinical knowledge, as they can be dissociated into each independent component process associated with anhedonia. An example of a response engendered by a conditioned motivator would be that of an alcohol addict to the sight or smell of alcohol, which can be uniquely manipulated to parse several component processes within a variety of tasks. Thus, the properties of conditioned motivators in anhedonia and the neural substrates underlying them will be critical in translating knowledge about these independent neuropsychiatric processes to the clinic. This review emphasizes the utilization of ‘reverse-translation’, integrating patient-based findings with preclinical animal models to experimentally parse component processes of anhedonia and develop holistic experimental models to measure it. Dissociating the independent, measurable component processes of anhedonia is critical for accurate representation in preclinical animal models and for acceleration of treatment strategies to the clinic.

Introduction
Healthcare systems have naturally relied on preclinical animal models to reveal potential indications of etiology and diagnosis, foster drug discovery, and guide treatment regimens in clinical populations. The term ‘translational research’ has been devised to describe this approach of exporting basic research findings into clinical practice. Although experimental animal models are indispensable in terms of informing future medical practice, clinical discoveries are evidently shaping the aims and direction of preclinical neuro-psychiatric research. Indeed, evolving diagnostic criteria and insights into the nature of clinical phenomena continue to refine our understanding of psychiatric illness. This method of drawing on patient-based findings to develop assays that measure the fundamental characteristics of clinically relevant symptoms in preclinical animal models is known as ‘reverse-translational research’.

Anhedonia presents as a fundamental symptom in many psychiatric disorders including major depression, substance dependence and schizophrenia, among others which affect significant portions of the population worldwide. Despite its prevalence, there has been limited success in developing novel treatments for anhedonia. One major reason for this dearth may be the lack of precision in preclinical animal models of anhedonia, the majority of which emphasize hedonic responses to primary reinforcers (rewards) such as palatable food, drugs of abuse, sex, and sociability. However, evidence suggests that human patients exhibiting anhedonia frequently display normal subjective reports of ‘liking’ for primary rewards. Rather, deficits in hedonic responding can be better characterized by responses to conditioned stimuli which have become associated with primary reinforcers through numerous contingent pairings, such as contextual or associative cues that signal reward. An example of a response engendered by a conditioned motivator would be that of an alcohol addict to the sight or presence of a beer bottle.

The following review emphasizes ‘reverse-translational’ strategies, integrating patient-based findings with preclinical models to experimentally parse component processes of anhedonia (see Figure 1) and develop holistic experimental models to measure it. Shortfalls from insufficient models are addressed and some existing examples of this strategy are highlighted including models that have provided insight into neurobiological mechanisms underlying anhedonia. Parsing anhedonia into its independent, measurable component processes is critical for accurate representation in preclinical animal models and for accelerating treatment strategies to clinical populations.

Dissociating Component Processes of Anhedonia
Exposure to rewarding stimuli stimulates memory consolidation and increases the prospect that behaviours that lead to reward will be performed in the future. Rewarding stimuli can be categorized as 1) primary rewards that are instictively and consciously...
pleasurable, including sexual intercourse, food, and drugs of abuse; and 2) secondary rewards—neutral stimuli that gain emotional value as they become reliable predictors or ‘cues’ of primary rewards through multiple contingent pairings.\textsuperscript{20,21} Despite pervasive assessment of primary rewards in preclinical animal models of anhedonia, responses to associative secondary rewards that require cognitive appraisal and specific learned behavioural responses may more accurately reflect the complexity of the human condition in ways that primary reward assays are not capable of capturing due to the nature of component processes underlying anhedonia.\textsuperscript{14,16,22}

Despite more than a century since anhedonia was originally defined as an “inability to feel pleasure”\textsuperscript{10} and the proposal of copious preclinical animal models to characterize it,\textsuperscript{11,12} therapeutic interventions remain only partially effective.\textsuperscript{10} This may be due to discrepancies between clinical anhedonia and representations of anhedonic-like phenotypes in preclinical animal models.\textsuperscript{12,24,25} Indeed, anhedonic patients often display normal affective reactions and subjective pleasure ratings relative to healthy controls.\textsuperscript{13,14} However, rodent models that induce anhedonic-like effects reliably observe deficits in sucrose consumption and drug intake suggesting that primary reward measures are not ideal for research into translational anhedonia. Furthermore, these deficits are consistently reversible by administration of common antidepressant medications.\textsuperscript{13,14} Which is paradoxical because as few as 30% of depressed patients with anhedonic features respond successfully to antidepressant drug regimens and treatment rates for substance abuse and schizophrenia are much lower.\textsuperscript{10,25}

Alternatively, blunted behavioural and neural responsivity are consistently observed in anhedonic individuals when assessed in tasks measuring anticipation and attentional capacity for cues that predict reward.\textsuperscript{11,13,14,20,27} Preclinical models measuring behavioural and neurophysiological responses to associative cues have demonstrated similar distinctions between primary and secondary rewards and further identified brain areas regulating behavioural abnormalities characteristic of anhedonia such as the basal ganglia and various mesolimbic structures.\textsuperscript{28,29} Interestingly, anhedonia often presents comorbidly with substance abuse, obesity and obsessive-compulsive disorders which share the common feature of increased incentive salience towards cues associated with reward.\textsuperscript{22,30,31} Thus, it is evident that widely used contemporary preclinical animal models do not accurately portray the intricacies associated with anhedonia in clinical populations.

Indeed, recent clinical evidence implicates multiple features of reward processing in anhedonia.\textsuperscript{16-18} These features can be parsed into multiple distinct component processes including affect,\textsuperscript{7,32} learning and memory,\textsuperscript{12,23} motivation\textsuperscript{18,23,24} and psychomotor factors\textsuperscript{25,26} that are each characterized by diverse neuropsychological mechanisms (Figure 1). Thus, deficits in responding for primary rewards may be attributed to dysfunction in any of these components and not necessarily affect. Although these processes can be experimentally dissociated in humans and nonhuman animals,\textsuperscript{22,27,33} preclinical models of anhedonia routinely only measure affective responses to primary rewards such as consumption of palatable food or self-administration of drugs of abuse.\textsuperscript{11,22,24} Nevertheless, complex associative-learning and approach-based (psychomotor activating, motivational) criteria are often implicit in tasks measuring affective ‘liking’ as subjects must learn correct behaviours that lead to reward. Similarly, behaviours may be misinterpreted due to ubiquitous, but often overlooked facets of reward anticipation and expectancy.\textsuperscript{11,13} These factors can be accounted for by implementing conditioned motivators in preclinical models. Conditioned motivators are the product of emotionally relevant learned associations that evoke approach-based and anticipatory behaviours and are importantly involved in each component process of anhedonia.\textsuperscript{40-42}

Thus, they represent a possible mediator for these theoretically independent mechanisms and an avenue for preclinical exploration.

**Figure 1.** Distinct component processes of anhedonia, their associated discrete neuropsychological mechanisms and possible behavioural measures for each.

**ROLE OF CONDITIONED MOTIVATORS IN COMPONENT PROCESSES OF ANHEDONIA**

Conditioned motivators are emotionally relevant associative stimuli that acquire meaningfulness from a previously neutral state because over multiple contingent pairings they come to reliably predict the presence or onset of pleasurable events.\textsuperscript{40,41} This transition involves affect, learned associations, as well as psychomotor and motivational components.\textsuperscript{40-42} In this way, conditioned motivators are inherently pleasurable, enhance memory consolidation and induce approach responses just as primary rewards do through increases in corticolimbic dopamine release.\textsuperscript{20,28,40,44-46} Consequently, conditioned motivators encompass the full spectrum of component processes pertinent to anhedonia, can be utilized in many available measures of reward processing and thus possess great translational potential.

Preclinical models of anhedonia demonstrate remarkable translatability when they use conditioned motivators in tasks that model symptomatology of human patients. For example, temporal and probabilistic reward tasks including fixed ratio or variable interval schedules of self-administration allocate ambiguity to associative cues by only occasionally reinforcing correct behavioural...
responses and can thus more appropriately distinguish changes in component processes as multiple domains of cognition and affect are involved.4,47 Additionally, responses for conditioned motivators in these tasks may more accurately reveal behavioural abnormalities of anhedonia due to the complex nature of learned associations between stimuli.14,16,22

Tests of conditioned approach including conditioned place preference and self-administration can similarly dissect many of the component processes underlying anhedonia using models of Pavlovian or instrumental conditioning.45,48 Using alcohol self-administration as a model, the drug can be deposited into a dish following successful responding and require additional approach responses to obtain the primary reward.49 Alternatively, alcohol can be directly infused intra-orally to dissociate flexible approach from uncompromising consummatory responses,50,53 or intracranially to reveal underlying neural circuitry or genetic changes associated with these responses. Moreover, cues such as a light or tone that predict reward availability can be integrated to further dissociate complex actions of conditioned motivators in anhedonia.45 As tasks assessing the multifaceted nature of anhedonia are more likely to translate findings to successful clinical treatments,44,47 and because conditioned motivators effectively comprise each component process of anhedonia, they represent primary importance in future preclinical and clinical research into the mechanisms underlying rewarded behaviour.

These similarities between conditioned motivators and primary rewards may underlie contradictory findings between preclinical animal models of anhedonia.51 For decades, the neurotransmitter dopamine was speculated to be involved in anhedonia exclusively through the processing of primary rewards.35,36,52 However, the function of dopamine has since been clarified to more accurately characterize its involvement in motivational, anticipatory and psychomotor aspects of reward processing.35,36,38,40,41,53,54 This has led to changes in the measurement of reward-related events, altered the scope of research into component processes of anhedonia and may help to more clearly interpret results across various preclinical laboratories.14,51,52

Accordingly, assessment of the properties of conditioned motivators in existing preclinical animal models of anhedonia will enhance the likelihood that convergent evidence proceeds efficiently to clinical treatment applications. Neuropsychological facets of learning and motivation must be integrated with affective measures to develop a more holistic view of anhedonia.

CONCLUSION

Translational strategies utilizing preclinical animal models are indispensable in realizing fundamental knowledge relative to neuropsychiatric care. Nevertheless, reverse-translational approaches are providing useful guidance to preclinical models, informing an increasingly comprehensive understanding of anhedonia and its dissociable component processes. Anhedonia can be parsed into multiple categories that conditioned motivators may fully encompass, and experiments exploiting subtle differences in responding for primary rewards vs. conditioned motivators may engender results directly relevant to complexities associated with the human condition. These conditioned motivators can be uniquely manipulated to parse several component processes within a variety of preclinical assays and thus will be crucial in effectively relaying knowledge between preclinical and clinical researchers in the future.

REFERENCES
19. Hernandez P, Sadeghian K, Kelley A. Early consolidation of instru-
31;84(3):436–52.
May;18(3):570-80.
Feb;22(2):116-27.
32. Franken I, Rassin E, Muris P. The assessment of anhedonia in clinical and non-clinical populations: further validation of the snath–hamilton
Feb;121(1):51.
40. Schultz W, Apicella P, Ljungberg T. Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of
41. De Houwer J, Thomas S, Baeyens F. Association learning of likes and dislikes: a review of 25 years of research on human evaluative condi-
1990;97:208-41.
44. Yin H, Ostlund S, Balleine B. Reward guided learning beyond dopamine in the nucleus accumbens: the integrative functions of cortico
Psychol Rev. 1984 Apr;91(2):251-68.
Jul;9(7):545-56.
Dec;54:107-43.
52. Thomsen K. Measuring anhedonia: impaired ability to pursue, experience, and learn about reward. Front Psychiatry. 2015 Sep;6:1409.
5;526(1):199-206.