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Invited essay

Animal to human translational paradigms relevant for approach avoidance conflict decision making

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ABSTRACT

Avoidance behavior in clinical anxiety disorders is often a decision made in response to approach-avoidance conflict, resulting in a sacrifice of potential rewards to avoid potential negative affective consequences. Animal research has a long history of relying on paradigms related to approach-avoidance conflict to model anxiety-relevant behavior. This approach includes punishment-based conflict, exploratory, and social interaction tasks. There has been a recent surge of interest in the translation of paradigms from animal to human, in efforts to increase generalization of findings and support the development of more effective mental health treatments. This article briefly reviews animal tests related to approach-avoidance conflict and results from lesion and pharmacologic studies utilizing these tests. We then provide a description of translational human paradigms that have been developed to tap into related constructs, summarizing behavioral and neuroimaging findings. Similarities and differences in findings from analogous animal and human paradigms are discussed. Lastly, we highlight opportunities for future research and paradigm development that will support the clinical utility of this translational work.

1. Introduction

Approach avoidance conflict has been described as situations involving "opposing and concomitant tendencies of desire … and of fear" [Millan, 2003] and has long been implicated as an important construct related to the experience of anxiety. There has been a surge of recent translational work related to approach-avoidance conflict, providing a potential link between findings from animal conflict paradigms and human behavior and symptomatology. The goal of the current review is to summarize findings from this research and provide potential paths towards furthering the clinical relevance of such translational work.

Animal research has been instrumental in characterizing potential neural substrates as well as pharmacological targets and treatments relevant for anxiety (Kalueff, Wheaton, & Murphy, 2007; Kumar, Bhat, & Kumar, 2013; Millan, 2003). Before human neuroimaging, animal research and human lesion studies were the primary methods for advancing neurobiological understanding of mental health. Animal research relies heavily upon behavioral tests and models that are thought to represent at least some aspect of mental health disorders. Beyond face validity, these paradigms have at least some predictive utility in terms of identifying pharmacologic agents or behavioral interventions that may be beneficial for human suffering (Cryan & Holmes, 2005; Millan & Brocco, 2003; Millan, 2003). The utility of animal paradigms is perhaps more evident within the anxiety disorders literature than other areas, with one of the prime examples being the translation of fear learning as modeled in animals to inform exposure therapy as implemented in humans (Craske, Hermans, & Vansteenwegen, 2006; Hermans, Craske, Mineka, & Lovibond, 2006; Hofmann, 2007, 2008; Vervliet, Craske, & Hermans, 2013). Animal research offers the experimental control to test neurobehavioral theories with a degree of control and precision that may not always be possible or ethical with human research. Thus, the use of animal research to inform clinical psychology work is incredibly important for continued advancement of the field.

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Given the above, the ability to generalize findings (or test for generalization) from animal to human work is paramount. However, there are many obstacles for such generalization. First, it is often difficult to identify which animal models or paradigms are most relevant for which human mental health disorders or symptoms (e.g., generalized anxiety versus panic, social anxiety, or even depression). Second, when various pharmacologic agents or manipulations show promise in animal models, it is difficult to identify which have the greatest potential for clinical treatment in human populations (Steckler, Stein, & Holmes, 2008). Third, it is not fully understood how neural targets identified in animal research generalize to the human brain that has non-equivocal differences in structure (e.g., the expansive prefrontal cortex) (Van der Worp et al., 2010). In addressing these challenges, we are often left with trying to compare apples to oranges, such as, comparing (a) how animal behavior changes with pharmacologic or behavioral manipulations to (b) how human self-report of symptoms changes with pharmacologic or psychotherapeutic intervention. Even when using neuroimaging, we are often comparing neural responses to passive viewing paradigms (i.e., symptom provocation studies) to how animal behavior changes with ablations or neurotoxic lesions. All too often, researchers must attempt to translate directly from animal studies to large clinical safety or efficacy studies without any bridging human research to more directly assess the translational potential of such findings (Steckler et al., 2008). In turn, animal researchers are faced with designing animal behavioral studies based on imperfect diagnostic profiles and self-report symptom dimensions.

The use of quantitative human behavioral paradigms that can objectively capture aspects of psychological disorders can be a powerful tool for translation of animal to human (or human back to animal) findings (Delgado, Olsson, & Phelps, 2006; Kumar et al., 2013; Young, Minassian, Paulus, Geyer, & Perry, 2007). Such paradigms are often developed from clinical or cognitive understanding of human function, which then leaves it to animal researchers to attempt to translate this into a viable animal test [as has been done with the continuous performance task (McKenna, Young, Dawes, Asgaard, & Eyler, 2013; Young et al., 2013);]. An additional strategy is to develop human analogues to currently-used animal paradigms. Here, we focus on opportunities for this latter strategy, with particular attention to paradigms that have been utilized to identify underlying neural substrates.

1.1. Approach-avoidance conflict

Prominent theories of motivated behavior propose three major systems: (1) a behavioral activation system, elicited by appetitive or rewarding stimuli, (2) a fight, flight, freeze system, elicited by threatening or aversive stimuli, and (3) a behavioral inhibition system, elicited by conflict between the other two systems, or approach-avoidance conflict (Corr, 2013; McNaughton & Gray, 2000). Approach-avoidance conflict arises when the same action is associated with both reward and punishment. Approach-avoidance conflict poses a unique decisional challenge for comparing the value of available options, because individuals must not only integrate information concerning the value of potential rewards and punishments, but also the likelihood and magnitude of those potential outcomes (Aupperle & Paulus, 2010; Quartz, 2009; Rolls & Grabenhorst, 2008). The importance of examining such conflict situations (in addition to fear responses alone) is apparent from animal research. For example, in rodent decision-making tasks amphetamine stimulates reward-seeking behavior when punishment is rare/non-existent, but drives avoidance behavior when punishments are prominent (Orsini, Moorman, Young, Setlow, & Floresco, 2015).

As we have discussed previously (Aupperle & Paulus, 2010), avoidance behavior in clinical anxiety disorders most often involves a decision to sacrifice potential rewards in order to avoid potential negative consequences. Avoidance that does not involve the sacrifice of potential rewards obviously exists, but would most likely not lead to a level of distress that would lead to an individual seeking treatment. For example, the fight, flight, freeze system may be highly relevant for panic attacks (i.e., acute fear responses to a situation); however, panic *disorder* only becomes a clinical problem when an individual starts sacrificing potential positive outcomes (e.g., not attending social events) in order to avoid the potential negative outcome of panic. For generalized anxiety disorder, overt avoidance behavior in response to acutely feared situations is often difficult to identify. Instead, individuals may engage in effortful behaviors (e.g., reassurance seeking) that allow them to continue approaching situations (e.g., going to work) while simultaneously preventing potentially feared negative outcomes. Therefore, approach-avoidance conflict and the behavioral inhibition system (rather than only the fear-flight-freeze system) may be particularly relevant for the understanding and treatment of anxiety disorders.

Animal research has a long history of relying on conflict- and exploratory-related paradigms to model anxiety. While human research has a long history of research dedicated to understanding approach and avoidance drives, much of this research has relied upon self-report measures and/or has focused on situations in which these two drives are not simultaneously occurring. There has recently been a surge of interest in developing conflict and exploratory paradigms that may have translational value in relation to animal tests, and that may be helpful in assessing anxiety-relevant conflict decisions and avoidance behavior. Below, we briefly summarize each of these types of animal paradigms, as well as the relevant neural networks and effects of anxiolytic medications (as this research may hold particular relevance for intervention efforts in humans). We then review paradigms that have been specifically developed to tap into related constructs in humans and summarize any neurobiological findings. Lastly, we highlight opportunities for future research and paradigm development to fill the gaps of this translational work.

Fear conditioning and extinction has served as an exemplary model of translational research in anxiety (Craske et al., 2006; Delgado et al., 2006; Hermans et al., 2006; Krypotos, Effting, Arnaudova, Kindt, & Beckers, 2014; Lommen, Engelhard, & van den Hout, 2010; Vervliet et al., 2013; van Meurs, Wiggert, Wicker, & Lissek, 2014). In these paradigms, subjects are typically presented with neutral stimuli either paired or not paired with an aversive event (e.g., delivery of shock) and behavioral and physiological outcomes are assessed. However, these paradigms are more relevant for the fight, flight, and freeze system rather than approach-avoidance conflict and either do not measure avoidance behavior *per se* (instead relying upon other behavioral and physiological responses, such as startle, eye blink, etc.), or do not examine avoidance behavior in the context of potential simultaneous reward. Similarly, passive viewing paradigms used during neuroimaging studies in humans only have indirect implications for avoidance, as behavioral responses are not assessed. Readers are referred to reviews related to these constructs and types of paradigms (Etkin & Wager, 2007; Sergerie, Chochol, & Armony, 2008; Shin & Liberzon, 2010; Vuilleumier & Pourtois, 2007). In this review, we focus on paradigms specifically measuring *behavior* in response to approach-avoidance conflict relevant decisions. While we do not claim to provide an exhaustive review of every test or model, we attempt to focus on categories of paradigms we feel may be particularly relevant for anxiety disorders, including (a) punishment-induced conflict paradigms, which involve situations in which the same behavior is associated with both reward and