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# Behaviourally inhibited temperament and female sex, two vulnerability factors for anxiety disorders, facilitate conditioned avoidance (also) in humans

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ABSTRACT

Acquisition and maintenance of avoidance behaviour is a key feature of all human anxiety disorders. Animal models have been useful in understanding how anxiety vulnerability could translate into avoidance learning. For example, behaviourally inhibited temperament and female sex, two vulnerability factors for clinical anxiety, are associated with faster acquisition of avoidance responses in rodents. However, to date, the translation of such empirical data to human populations has been limited since many features of animal avoidance paradigms are not typically captured in human research. Here, using a computer-based task that captures many features of rodent escape-avoidance learning paradigms, we investigated whether avoidance learning would be faster in humans with inhibited temperament and/or female sex and, if so, whether this facilitation would take the same form. Results showed that, as in rats, both vulnerability factors were associated with facilitated acquisition of avoidance behaviour in humans. Specifically, inhibited temperament was associated with higher rate of avoidance responding, while female sex was associated with longer avoidance duration. These findings strengthen the direct link between animal avoidance work and human anxiety vulnerability, further motivating the study of animal models while also providing a simple testbed for a direct human testing.



## 1. Introduction

### 1.1. Behavioural avoidance

Behavioural avoidance is often an adaptive strategy in daily life, which can prevent or reduce the impact of potentially aversive events and actions (e.g., stopping at a red light to avoid an accident). However, in some cases, emphasis on avoiding sources of possible harm can contribute to the development of a psychopathology. Indeed, avoidance behaviour is a predominant symptom in all anxiety disorders (DSM-IV; American Psychiatric Association, 1994), and it often distinguishes between those who develop a disorder following an exposure to stressors and those who recover (O'Donnell et al., 2007; Karamustafalioglu et al., 2006; Marshall et al., 2006; North et al., 1999; Barlow, 2002). In spite of such a crucial role of avoidance behaviour in human anxiety disorders, most of the relevant literature on how avoidance behaviour develops and is maintained is based on research with non-human animals (Dymond and Roche, 2009).

### 1.2. Escape-avoidance in non-human animals

In rats, avoidance paradigms often involve a warning signal (e.g., a light or tone) that precedes the occurrence of an aversive event (e.g., electric shock). The rats first learn to terminate the aversive event by making an adequate protective response (escape response; ER). Gradually, they learn the association between the warning signal and the aversive event, and come to exhibit the protective response during the warning signal but before onset of the

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aversive event, which results in omission of that aversive event (avoidance response; AR).

The acquisition and extinction of ARs show considerable individual differences. For instance, inbred Wistar–Kyoto (WKY) rats are highly stress-reactive and exhibit withdrawal responses in social and non-social situations, such as low activity in the open field and the forced-swim test (Pare, 1994). Due to such reserved response in the face of novel situations, WKY rats are often used as an animal model for behaviourally inhibited temperament (Servatius et al., 2008). Interestingly, in spite of the lack of mobility commonly associated with this strain, WKY rats acquire lever-press ARs at an accelerated rate and to a higher asymptotic level than outbred Sprague-Dawley (SD) rats (Servatius et al., 2008). In addition to strain differences, there are also sex differences; specifically, female rats often show facilitated acquisition of the ARs relative to males of the same strain (Beck et al., 2010; Beatty and Beatty, 1970; Van Oyen et al., 1981). Since both female sex and inhibited temperament are vulnerability factors for anxiety disorders in humans (Gladstone et al., 2005; Clauss and Blackford, 2012; Essex et al., 2010; Wittchen and Hoyer, 2001; Zhang and Ho, 2011; Chronis-Tuscano et al., 2009; Gudino, 2013; Pigott, 1999; Rosenbaum et al., 1993), these findings suggest a possible mechanism – facilitated acquisition of avoidance behaviour – that mediates vulnerability to anxiety disorders in humans.

### 1.3. Avoidance in humans

To date, the translation of animal models of avoidance to human clinical research has been limited by a lack of tools for measuring human avoidance behaviour in a laboratory setting. So far, human avoidance behaviour has been assessed mainly by subjective self-report questionnaires (e.g., Taylor and Sullman, 2009; Sheynin et al., 2013; Cloninger, 1986), which directly query the respondent about the type and frequency of avoidant behaviours, and then assign a point score based on these answers. Such approaches are subject to all the limitations of self-report, including the opportunity for people to falsify or withhold information, and the possibility that people may not be able to accurately or objectively assess their own behaviour. Questionnaires that probe past behaviour patterns also, of course, are unable to directly assess how these behaviours are acquired.

In attempts to more directly evoke and evaluate avoidance learning, several human studies have used mild ("unpleasant but bearable") electric shocks (e.g., Delgado et al., 2009; Lovibond et al., 2008), or aversive visual or auditory stimuli (e.g., Dymond et al., 2011) as the aversive events that could be avoided. For instance, Lovibond et al. (2008) have considered paradigms in which human subjects make responses to avoid electric shock; their data provide support of an expectancy-based model of avoidance and anxiety, in which ARs are executed to attenuate the expectancy that one develops for an upcoming aversive event. Lovibond's procedure consists of a 5-s visual warning signal followed by a 10-s delay interval and a period of a possible shock that could be avoided by pressing a specific key (the AR). Self-reported shock expectancy and skin conductance were recorded during the delay interval and were shown to decrease as the AR was acquired, suggesting a mechanism for anxiety reduction by avoidance performance. Furthermore, Lovibond et al. (2009) used a similar procedure to demonstrate how execution of ARs can prevent individuals from extinguishing fear conditioning, as well as to suggest a common cognitive mechanism in classical and instrumental aversive conditioning (Lovibond et al., 2013).

Although such methodologies add to our understanding of avoidance behaviour, it has also been argued that, due to ethical considerations, the aversive stimuli such as electric shock used in most human avoidance paradigms are too mild to effectively produce a conditioned response (Arcediano et al., 1996). In addition, in many cases, human participants are explicitly informed about the AR at the beginning of the experimental session, meaning that the experiment investigates participants' ability to perform ERs and ARs, rather than how participants learn to acquire these responses (e.g., Molet et al., 2006; Lovibond et al., 2008).

### 1.4. Computer-based tasks and the current study: bridging the gap

Another line of human studies has considered computer-based tasks, some of which take the form of a spaceship videogame. For example, in one such design (Molet et al., 2006), participants control a spaceship and attempt to gain points by destroying an enemy that appears on the screen. During the task, warning signals appear and predict an on-screen aversive event (e.g., point loss and destruction of the player's avatar). Participants can avoid this aversive event by moving the spaceship to designated "safe areas" on the screen during the warning period. The idea here is that, even though no physiologically aversive stimulus (e.g., electric shock) is delivered, people are nonetheless generally motivated to avoid aversive events within the game. Variations of such tasks have been successfully used to test passive avoidance (Arcediano et al., 1996), active avoidance (Molet et al., 2006), differential effects of reinforcement contingencies and contextual variables (Raia et al., 2000), and discriminative learning and context-dependent latent inhibition (Byron Nelson and del Carmen Sanjuan, 2006). However, none of those studies analyzed escape behaviour or the transition from ER to AR, nor have they tried to replicate the rat studies which show accelerated avoidance acquisition as a function of inhibited temperament or female sex.

Accordingly, in the current study, we have used a videogame task, based on that of Molet et al. (2006), to study avoidance acquisition, including the transition from ER to AR, in healthy humans with and without the vulnerability factors of inhibited temperament and female sex. We hypothesized that, as observed in rats, inhibited participants would demonstrate faster learning to escape from and/or avoid the aversive events in the current task. Consistent with the animal results, we further hypothesized that females might show similar effects. We were also interested in whether each vulnerability factor could independently promote acquisition and expression of avoidance, or whether the two factors might differentially contribute to specific aspects of avoidance behaviour.

## 2. Methods

### 2.1. Participants

Participants were 102 healthy young adults (Rutgers University-Newark undergraduate students; mean age 21.0 years, SD 4.3; 62.7% female). Seventy-one participants (69.6%) were recruited via a departmental subject pool, in which available research studies are posted and students sign up to participate in exchange for research credits in a psychology class. The remaining thirty-one participants (30.4%) were recruited via flyers posted around the campus and received cash payments in the amount of $20. No significant differences were observed between participants that received cash vs. those that received credits, on any behavioural, demographic, or questionnaire measure (all $p > 0.050$); analyses were therefore pooled over all 102 participants. Participants were tested individually; the participant and experimenter sat in a quiet testing area during the experiment. All participants provided written informed consent and the experiment was approved by the local research ethics committee and conducted in accordance with guidelines