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D-Cycloserine for the augmentation of an attentional training intervention for trait anxiety

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ABSTRACT

The present study investigates the combination of two novel strategies for the treatment of anxiety that resulted from translational research. We examined whether the putative memory enhancer, D-cycloserine (DCS), offered benefit to procedures designed to train attention away from threat. Participants were 44 adults selected on the basis of high trait anxiety. In this randomized study, DCS or placebo was administered 1 h prior to attentional training away from threat using the dot probe task. On the following day, the effectiveness of this training was assessed along with emotional reactivity following two stressful tasks. We found that the addition of DCS resulted in significantly stronger reduction in attentional bias toward threat relative to placebo, but found no additive effects for the DCS condition on subsequent emotional reactivity. These results provide initial support for the efficacy of DCS for augmenting attentional training tasks; potential strategies for enhancing these results are discussed.

1. Introduction

Despite the successes of cognitive-behavioral and pharmacologic interventions for the treatment of anxiety disorders, many patients continue to need additional or alternative treatment (Hofmann & Smits, 2008; Pollack et al., 2008). Two recent translational research successes – attentional training interventions and the use of D-cycloserine (DCS) to augment exposure-based cognitive-behavioral therapy (CBT) – have shown promise as innovative strategies for the treatment of anxiety disorders.

Attentional training interventions emerged from basic research demonstrating elevated vigilance toward threatening cues (attentional bias) among individuals with anxiety disorders or sub-syndromal anxiety symptoms (for a review, see Bar-Haim, Pergamin, Bakermans-Kranenberg, & van Ijzendoorn, 2007). In a seminal study, MacLeod, Rutherford, Campbell, Ebsworthy, and Holker (2002) found that training individuals to attend to threatening stimuli led to enhanced emotional reactivity during a subsequent stressful task. This study both provided evidence for a causal effect of vigilance toward threat on emotional reactivity, and support for the possibility of using a training procedure to modify attentional bias. Attentional training consists of a computerized task that provides repeated presentations of stimulus pairs (one threatening and one neutral) with one type of stimulus followed more frequently by a target stimulus, thus training early attentional allocation either toward or away from the threatening information.

Early applications of this strategy demonstrated that the training procedure modified both attentional bias and emotional reactivity to stress (MacLeod et al., 2002; See, MacLeod, & Bridle, 2009). Several investigators have recently applied this strategy to the treatment of various anxiety conditions by randomly assigning individuals to a condition in which they receive attentional training away from threat stimuli or to a placebo training condition. Results have consistently shown that attentional training is associated with reduced attentional bias and positive effects on diagnostic or behavioral indices of anxiety. For example, Amir, Beard, Burns, and Bomyea (2009) randomly assigned 29 treatment-seeking individuals with GAD to eight sessions of either attention modification or to a placebo training procedure. Results indicated a decrease in both attentional bias toward threat and disorder-specific symptoms for the attentional training group as compared to the placebo training group. Similarly, Hazen, Vasey, and Schmidt (2009) randomly assigned 24 severe worriers to receive five sessions of either attention retraining or to a sham training procedure. Results indicated that compared to the shame training condition, participants in the attention retraining condition evidenced significant reductions in both attentional bias to threat and symptoms of anxiety and depression.

Similar results have been reported for the use of attentional training for social anxiety. Amir, Weber, Beard, Bomyea, and Taylor (2008) randomly assigned 94 socially anxious undergraduate stu-

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dents to either an attention modification or placebo training procedure that was completed in a single day. They reported that in comparison to participants in the placebo training condition, participants in the attention modification condition evidenced lower levels of anxiety in response to a public speaking challenge, and were rated as having given higher quality speeches. Similarly, Schmidt, Richey, Buckner, and Timpano (2009) randomly assigned 36 individuals with social anxiety disorder to an attention training or control condition, and found that compared to control participants, participants receiving attention training evidenced significantly greater reductions in social anxiety and trait anxiety, and that 72% of participants in the attention training condition no longer met diagnostic criteria for social anxiety disorder (as compared to 11% of participants in the control condition). Together, these results support the hypothesis that attention plays a causal role in anxiety conditions, and provide strong evidence in favor of attention training procedures for the reduction of anxiety symptoms.

The mechanism of action of attentional training interventions is not well understood at this early stage of its evaluation. One hypothesis is that these procedures create change through repeated exposure to an attentional contingency that can ameliorate preexisting cognitive processing biases (MacLeod, Koster, & Fox, 2009). With a reduced attentional bias toward threat, the cascade of anxiogenic responses to threat cues is hypothesized to decrease, thereby interrupting the self-perpetuating cycles that characterize the anxiety disorders (see Amir et al., 2009).

In a separate advance in translational research, D-cyloserine (DCS), a partial agonist at the NMDA receptor in the amygdala, has been shown to augment extinction learning in animal and human paradigms (see Davis, Myers, Ressler, & Rothbaum, 2005; Richardson, Ledgerwood, & Cranney, 2004). A number of trials support the efficacy of DCS as a way to enhance the therapeutic learning provided by exposure-based CBT (Norberg, Krystal, & Tolin, 2008), with the use of individual doses of DCS taken prior to exposure sessions showing benefit relative to placebo for the treatment of acrophobia (Ressler et al., 2004), social phobia (Guastella et al., 2008; Hofmann et al., 2006), panic disorder (Otto et al., 2010), and obsessive-compulsive disorder (Kushner et al., 2007; Wilhelm et al., 2008).[2]

DCS appears to exert its beneficial effects by aiding the consolidation of extinction learning (Davis et al., 2005; Richardson et al., 2004), but the generality of these memory effects is not yet clear. DCS has performed poorly in applications of this single-dose paradigm to non-emotional memory tasks that do not involve extinction in humans (Otto et al., 2009; Goff et al., 2008). However, animal models have suggested that DCS facilitates other types of memory in tasks that may involve limbic activation, such as spatial memory (Land & Riccio, 1999; Lelong, Dauphin, & Boulouard, 2001) and taste aversion acquisition (Davenport & Houpt, 2009; Nunnink, Davenport, Ortega, & Houpt, 2007). Similarly, in humans, a recent study showed that DCS can facilitate the retention of fear conditioning using mild electric shock as a stimulus (Kalisch et al., 2009).

Attentional biases such as those manipulated in the attentional training tasks have been associated with both cortical and subcortical neural activation, including activation of the amygdala (e.g., van den Heuvel et al., 2005). Moreover, at the neuronal level, there is some evidence for a role of NMDA receptors in competitive attention (e.g., Deco & Rolls, 2005). Finally, it has been proposed that DCS may act preferentially on implicit extinction learning rather than on cognitively-mediated processes (Grillon, 2009); hence, the implicit conditioning of responses away from threat cues, as likely occurs in attentional training (see Van Damme, Crombez, Hermans, Koster, & Eccleston, 2006), may be a mechanism open to DCS modulation.

The present study targets the confluence of two lines of translational research. First, the training of attentional bias away from threat has potential as a novel treatment of anxiety disorders and may operate through retraining of associative learning networks that are, at least in part, amygdala-based. Second, in repeated small-scale trials DCS augmentation has shown clinical benefit. It remains unclear whether DCS has therapeutic applications other than extinction learning, although there are encouraging findings for other emotional associative learning paradigms. Accordingly, this investigation has two primary aims: (1) replication of the findings from MacLeod and colleagues (2002) indicating a change in attentional bias and emotional reactivity subsequent to modification of attentional bias, and (2) evaluation of the efficacy of DCS relative to placebo for the augmentation of this intervention. Consistent with previous findings (e.g., Amir et al., 2008), we hypothesized that participants would exhibit reductions in attentional bias and emotional reactivity following the attentional training procedure. In addition, we hypothesized that participants receiving DCS would exhibit greater decreases in attentional bias following training relative to those receiving placebo, and that participants receiving DCS would exhibit greater reductions in emotional reactivity to stressful tasks relative to those receiving placebo. Although many current applications of attentional training utilize multiple sessions (e.g., Amir et al., 2009), we selected a single session in training to be consistent with MacLeod et al. (2002) and to be consistent with the limited number of exposure sessions used in trials of DCS augmentation (e.g., Ressler et al., 2004).

2. Methods

2.1. Participants

Adults between the ages of 18–65 were recruited from the greater Boston area through newspaper advertisements, flyers, and internet postings. Potential participants were excluded if they reported being pregnant or nursing, had a history of memory or cognitive impairment, or if they were taking any prescription psychotropic medications or medications contraindicated with DCS. Criteria for inclusion in the study included a score of 50 or higher on the State-Trait Anxiety Inventory-Trait Version (STAI-T; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), which was administered as part of a telephone screen. A score of 50 on the STAI, which is 1.5 standard deviations above the mean for the general population, was selected to reflect an elevated level of trait anxiety and is consistent with recruitment of high trait anxious individuals in previous investigations (e.g., Wilson & MacLeod, 2003). No other evaluation of anxiety or Axis I conditions was conducted during the phone screen or physician evaluation. Eligible participants were evaluated by the prescribing physician prior to engaging in any laboratory procedures. Upon medical approval, participants were invited to the laboratory for two experimental sessions on two consecutive days. Participants were compensated $50 for the completion of all study procedures.

Forty-four participants (23 women) provided written informed consent and were enrolled in the study. The mean age of study participants was 44.5 years (SD = 12.4, range = 18–65). Participants in the sample were 45.5% Caucasian, 41% African-American, 7% Hispanic, and 4.5% Asian, with 2% of participants electing to not indicate their race/ethnicity.

[2] Studies on the effects of DCS in the treatment of OCD are more equivocal than for other anxiety conditions. See, for example, Storch et al. (2007).