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D-Cycloserine facilitates extinction learning and enhances extinction-related brain activation

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ABSTRACT

Extinction learning is modulated by N-methyl D-aspartate receptors (NMDAR) particularly in prefrontal and hippocampal brain regions. The use of of NMDA agonists in exposure therapy of anxiety disorders has been investigated in various patient groups. Behavioral results showed beneficial effects of pre-learning administration of the partial NMDAR agonist D-Cycloserine (DCS) on therapy success. However, the impact of DCS upon non-fear-related contextual extinction, and associated recruitment of extinction-relevant brain regions is as yet unknown. In the present fMRI study, healthy human participants performed a context-related associative learning and extinction task. A single dose of DCS, administered prior to extinction learning, enhanced extinction learning performance in an identical context, and increased activation in prefrontal, temporal as well as hippocampal/insular regions, compared to placebo controls. In contrast, DCS did not affect extinction learning in a novel context, nor the renewal effect, which describes the recovery of an extinguished response if the context of extinction differs from the context of recall. Our findings demonstrate a specific involvement of prefrontal and hippocampal NMDAR in the modification of established stimulus-outcome associations in identical contexts and thus their role in behavioral flexibility, underlining their potential for enhancing AAA extinction learning.

1. Introduction

Extinction learning is an important behavioral phenomenon that allows the organism to adapt its behavior to changed situations. In extinction learning, a process which appears to be based on new inhibitive or integrative learning rather than unlearning (Bouton, 2002; Phelps, Delgado, Nearing, & LeDoux, 2004), a new memory trace is formed that competes with the initial memory (Bouton, 2002; Quirk & Mueller, 2008). For selecting the proper response, context consideration is crucial (for review see Rosas, Todd, & Bouton, 2013).

The context-dependency of extinction is impressively illustrated by the post-extinction phenomenon *renewal*, which describes the recovery of a previously extinguished response when the test context differs from the extinction context (Bouton & Bolles, 1979). By coupling learning success to the therapeutic context, the renewal effect can constitute a major challenge for the therapy of anxiety or PTSD disorders. Thus, improvement of maladaptive learning processes as well as generalization of learned adaptive behavior to other contexts is of considerable interest to both basic and clinical researchers.

Successful (fear) extinction learning and its consolidation is based on activation in a wide-spread brain network which comprises prefrontal cortex (PFC) as well as hippocampal and amygdalar regions (for review see Sehlmeyer et al., 2009). Moreover, extinction learning and memory depends, among others, on glutamatergic neurotransmitter activation. *N*-methyl-D-aspartate receptors (NMDAR) are considered a main candidate for modulating extinction learning and renewal (for review see Myers & Davis, 2002). First evidence of NMDAR dependent extinction processes were provided by animal studies, which demonstrated significant impairments in diverse learning and memory processes induced by NMDAR blockade (Kim, DeCola, Landeira-Fernandez, & Fanselow, 1991; Xu, Russell, Bazner, & Hamilton, 2001; for review see Riedel, Platt, & Micheau, 2003). Infusion of NMDAR antagonists into prefrontal brain areas also caused significant deficits in extinction and reversal learning (Bohn, Giertler, & Hauber, 2003; Lissek & Güntürkün, 2003; Quirk & Mueller, 2008) as well as in consolidation of extinction (Baker & Azorlosa, 1996; Burgos-Robles, Vidal-Gonzalez, Santini, & Quirk, 2007; Santini, Muller, & Quirk, 2001; Sotres-Bayon, Diaz-Mataix, Bush, & LeDoux, 2009; for review see Davis, 2011).

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Complementary to the effects of NMDAR blockade, the administration of NDMA agonists was found to enhance extinction learning and its consolidation (for review see Fitzgerald, Seemann, & Maren, 2014). After promising results in rats, which indicated enhancing effects of the partial NMDA agonist D-Cycloserine (DCS) in fear extinction (e.g. Ledgerwood, Richardson, & Cranney, 2003; Walker, Ressler, Lu, & Davis, 2002), researchers discovered DCS as a potential pharmacological support for exposure therapy, a therapeutic method analogous to extinction. Since then, clinical implications of pre-learning DCS administration were investigated in different patient groups, demonstrating significant beneficial effects of combined DCS/exposure treatment compared to placebo/exposure treatment. Indeed, enhancing DCS effects upon extinction were reported for patients suffering from acrophobia (Ressler, Rothbaum, Tannenbaum, & Anderson, 2004; Smits, Rosenfield, Otto, Powers, et al., 2013), social anxiety (Hofmann, Pollack, & Otto, 2006; Smits, Rosenfield, Otto, Marques, et al., 2013), panic (Otto et al., 2010) as well as obsessive compulsive disorder (OCD; Kushner et al., 2007; Wilhelm et al., 2008). Nonetheless, some studies failed to find an effect of DCS in clinical populations, although statistical trends were detected (spider phobia: Guastella, Lovibond, Dadds, Mitchell, & Richardson, 2007; agoraphobia/panic disorder: Siegmund et al., 2011; OCD: Storch et al., 2007).

Whereas most patient studies found promising DCS pharmacotherapeutic effects upon lasting fear reduction in individuals, studies with healthy human participants are still rare and yielded contradictory results: Whereas a single dose of DCS (250 mg) enhanced declarative learning in healthy human participants (Onur et al., 2010), no significant effects on memory tasks were observed after administration of a weekly dose of 50 mg DCS (Otto, Basden, & Mchugh, 2009). Likewise, inconsistent DCS effects were reported in the extinction of conditioned fear in healthy participants. While single doses of 50, 250 or 500 mg of DCS yielded no significant effects in fear extinction (Guastella, Dadds, Lovibond, Mitchell, & Richardson, 2007; Guastella, Lovibond, et al., 2007; Klumpers et al., 2012), a 100 mg DCS dose enhanced extinction learning (Kuriyama, Honma, Soshi, Fujii, & Kim, 2011). The meta analysis by Rodrigues et al. (Rodrigues et al., 2014) summarizes those contrasting observations by highlighting beneficial DCS effects on human extinction learning particularly at low doses (25–250 mg). Moreover, post-learning DCS administration also revealed beneficial effects and improved extinction memory consolidation in animals (Bouton, Vurbic, & Woods, 2008; Ledgerwood et al., 2003; Woods & Bouton, 2006). Similar enhancements were also demonstrated in human patients suffering from acrophobia (Smits, Rosenfield, Otto, Powers, et al., 2013). Importantly, the observed clinical improvement was moderated by the success of extinction learning: Patients who reached a low anxiety level at the end of the extinction/exposure session showed a significantly greater enhancement than patients whose anxiety levels remained high. Also non-clinical trials demonstrated enhancing effects in fear extinction memory consolidation after post-learning DCS administration, evidenced by increased skin conductance responses (Kalisch et al., 2009). Thus, DCS can be described as a cognitive enhancer that interacts with the extinction learning process to boost behavioral extinction *and* consolidation (for review see Vervliet, 2008).

In view of this therapeutic success, we here investigate the behavioral and neuronal effects of DCS on extinction learning without a fear component. Up to now, the underlying neural mechanisms have rarely been investigated. We only know from recent studies that enhanced declarative learning induced by DCS was associated with significantly increased hippocampal activation (Onur et al., 2010). In accordance, Kalisch and colleagues (Kalisch et al., 2009) observed enhancing effects of DCS in fear memory consolidation as well as increased activation in the posterior hippocampus/collateral sulcus region and in the medial prefrontal cortex – brain regions that are known to mediate extinction and renewal (Golisch, Heba, Glaubitz, Tegenthoff, & Lissek, 2017; Lissek, Glaubitz, Güntürkün, & Tegenthoff, 2015; Lissek, Glaubitz, Schmidt-Wilcke, & Tegenthoff, 2016; Lissek, Glaubitz, Uengoer, & Tegenthoff, 2013; Lissek, Glaubitz, Wolf, & Tegenthoff, 2015).

However, to the best of our knowledge, there are no studies as yet that combine DCS and functional magnetic resonance imaging (fMRI) to explore potential effects upon the extinction-related phenomenon of renewal. Up to now, we only know that in animals, DCS reduces spontaneous recovery (Ledgerwood et al., 2003; Walker et al., 2002) as well as reinstatement (Ledgerwood, Richardson, & Cranney, 2004), but not rapid reacquisition (Ledgerwood, Richardson, & Cranney, 2005) or renewal (Woods & Bouton, 2006) (for review see Vervliet, 2008).

To assess the effects of DCS upon the processing of contextual extinction learning and renewal in healthy human participants, we used an associative learning task, in which participants were required to learn relations between stimuli and outcomes presented in different contexts, which were reversed during extinction learning. This predictive learning task (Üngör & Lachnit, 2006), which we already used in previous studies (Golisch et al., 2017; Lissek, Glaubitz, Güntürkün, et al., 2015; Lissek, Glaubitz, Wolf, et al., 2015; Lissek et al., 2013, 2016), features an ABA design suited to evoke renewal, combined with a control AAA condition that does not evoke renewal. Healthy volunteers received a single dose of the NMDAR agonist DCS or a placebo prior to extinction learning of previously acquired associations. Based on earlier findings, we predicted that DCS would enhance extinction learning performance, relative to placebo. Furthermore, it is conceivable that a better extinction learning performance may also influence renewal rates. However, since as of today little is known about the effects of DCS on human renewal and thus a directional hypothesis cannot be derived from the literature. Moreover, we hypothesized that the enhancement in extinction learning would be associated with increased brain activation in regions that are highly involved in context-related extinction learning and have a high density of NMDAR, such as prefrontal cortex and hippocampus.

2. Materials and methods

2.1. Participants

Fifty-two healthy right-handed volunteers (24 males, 28 females) participated in this study. Four subjects had to be excluded due to weak learning performance (i.e. overall percentage of correct responses during acquisition <70%) or inadequate datasets, including signal or movements artifacts. All reported analyses are calculated from the final sample of 48 participants with 24 subjects per group (21 males, 27 females). Participants were randomly allocated to the experimental D-Cycloserine (DCS) or control placebo (PLAC) group; mean age within the groups was 23.79 years ± 0.84, range 19–35 years in DCS and 25.29 years ± 0.70, range 20–31 years in PLAC. All participants had normal or corrected-to-normal vision; none had any current neurological and medical condition.

Subjects participated in the present study after giving written informed consent. The protocol was approved by the local ethics board of the Ruhr-University Bochum and conforms to the Code of Ethics of the World Medical Association (Declaration of Helsinki). Prior to the experiment, participants received handouts informing them about the pharmacological properties of the NMDAR agonist D-Cycloserine, its general clinical use and the fMRI