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Deficient inhibitory processing in trait anxiety: Evidence from context-dependent fear learning, extinction recall and renewal

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ABSTRACT

Background: Impaired fear inhibition has been described as a hallmark of pathological anxiety. We aimed at further characterizing the relation between fear inhibition and anxiety by extending previous work to contextual safety stimuli as well as to dimensional scores of trait anxiety in a large sample.
Methods: We employed a validated paradigm for context-dependent fear acquisition/extinction (day 1) and retrieval/expression (day 2) in 377 healthy individuals. This large sample size allowed the employment of a dimensional rather than binary approach with respect to individual differences in trait anxiety.
Results: We observed a positive correlation on day 1 between trait anxiety with all CSs that possess an inherent inhibitory component, conveyed either by reliable non-reinforcement of a specific CS in a dangerous context (safe cue) or by the context itself (i.e., safe context). No correlation however was observed for a CS that possesses excitatory (threatening) properties only. These results were observed during fear learning (day 1) for US expectancy and fear ratings but not for SCRs. No such pattern was evident during fear and extinction retrieval/expression (day 2).
Conclusion: We provide further evidence that high trait anxiety is associated with the inability to take immediate advantage of environmental safety cues (cued and contextual), which might represent a promising trans-diagnostic marker for different anxiety disorders. Consequently, the incorporation of methods to optimize inhibitory learning in current cognitive behavioral therapy (CBT) treatments might open up a promising avenue for precision medicine in anxiety disorders.
Limitations: We did not include patients diagnosed with anxiety disorders.

1. Introduction

Fear reactions can be innate or acquired through experiences (Rachman, 1977). In changing environments it is particularly critical for survival and self-preservation to learn about potential environmental dangers and predictors thereof, as well as about safety signals. To this end, the prediction of future events allows for the appropriate initiation of emotional and physical reactions.

Fear conditioning is widely used in the laboratory to model these learning processes. In differential fear conditioning, a neutral object (conditioned stimulus, CS+) that has been associated with an aversive event (unconditioned stimulus, US) can be distinguished from any other occurring (safe) stimuli (CS−). Conditioned fear responses (conditioned response, CR) to the CS+ thereby represent adaptive responses to real environmental threats. These anticipatory threat responses are however confined through safety learning processes that allow for the identification of non-dangerous cues (e.g., the CS−) or contexts signaling safety. In addition, the adaptation of initially learned contingencies to changing environmental demands can be advantageous in scenarios where a danger cue has lost its predictive value (i.e. extinction learning, Craske et al., 2008).

Consequentially, not only exaggerated reactions to threat signals, but also deficits in learning or processing of safety signals can lead to maladaptive fear responses, i.e., responses that are disproportional and/or contextually inappropriate (Mineka & Zinbarg, 2006) or generalize to innocuous stimuli (Dymond, Dunsmoor,

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Vervliet, Roche, & Hermans, 2015). During the past years, the importance for adaptive responding of the latter inhibitory safety learning processes has gained increasing attention (Kong, Monje, Hirsch, & Pollak, 2014; Pollak, Monje, & Lubec, 2010), and pathological anxiety has been linked to deficits in inhibitory fear processing and/or maladaptive stimulus generalization during fear learning (Gazendam, Kamphuis, & Kindt, 2013; Haddad, Pritchett, Lissek, & Lau, 2012; Indovina, Robbins, Núñez-Elizalde, Dunn, & Bishop, 2011; Kindt & Soeter, 2014), extinction (Gazendam et al., 2013; Sehlmeyer et al., 2011) and return of fear (Kindt, Soeter, & Vervliet, 2009; Kindt & Soeter, 2013; Soeter & Kindt, 2010). However, these results (Martínez et al., 2012; Torrents-Rodas et al., 2013) and results based on other measures of negative affect (Fredrikson & Georgiades, 1992; Otto et al., 2007; Pineles, Vogt, & Orr, 2009) are not unequivocal with respect to the impact of anxiety levels on fear-related processes.

With this study, we aim at further characterizing behavioral and autonomic correlates of inhibitory safety learning processes to cued and contextual stimuli in anxiety using trait anxiety as a proxy, as it is an established risk factor for pathological anxiety (Chambers, Power, & Durham, 2004). Trait anxiety reflects an individual's disposition to experience anxiety-relevant emotions and to express anxiety-related behaviors to a wide range of (unspecific) stimuli (Spielberger, Gorsuch, & Lushene, 1983) and has also been linked to inhibitory processing deficits in other paradigms (Basten, Stelzel, & Fiebach, 2011; Berggren & Derakshan, 2014; Luo, Gu, & Huang, 2011).

To date, research on the relationship between trait anxiety and fear conditioning and extinction has been limited to cue conditioning and conditioned cue inhibition paradigms, and studies investigating the modulatory role of the context (such as Glotzbach-Schoon et al., 2013) are eagerly awaited. This is of critical importance, as anxiety has been linked to a tendency for context conditioning (Grillon, 2002) and as fear extinction has been shown to be inherently bound to the context in which (extinction) learning takes place (Bouton, 2004; Bouton & King, 1983; Maren, Phan, & Liberzon, 2013).

In previous studies investigating an association between conditioning/extinction and trait anxiety, dichotomous classifications have mostly been employed (such as median-split Haddad et al., 2012; Kindt & Soeter, 2014) or recruitment of extreme groups (Gazendam et al., 2013; Torrents-Rodas et al., 2013) while only few studies have employed truly dimensional approaches (Indovina et al., 2011; Martínez et al., 2012; Sehlmeyer et al., 2011).

This study thus aims to fill these gaps by investigating context-dependent excitatory and inhibitory learning within the *Negative Valence Systems* (i.e. lower-order constructs: potential and acute threat) of the RDoc Matrix (Cuthbert & Insel, 2013), and their association with the dimensional phenotype trait anxiety (from extremely low to clinically relevant scores) in the largest sample studied to date ($N = 377$).

We employed an established paradigm (Lonsdorf et al., in press; Kalisch et al., 2006; Haaker et al., 2013) including context-dependent differential fear conditioning and extinction learning (day 1) as well as a recall/retrieval session (day 2), using two units of analysis (self-reports of fear and US expectancy; psychophysiology). This paradigm allows for testing subjects' ability to identify two structurally different sources of safety information: the cue itself (the CS− that is never followed by a US) and, the context (the extinction context, in which even the former CS+ is reliably not followed by the US). In particular, as the same visual cue (CS+) in the paradigm can either signal danger or safety dependent on the context (the conditioning and the extinction context, respectively), the discrimination between danger and safety cannot be made based on perceptual properties of the CS, as in other paradigms (Jovanovic et al., 2013; Lissek et al., 2014), but relies on contextual

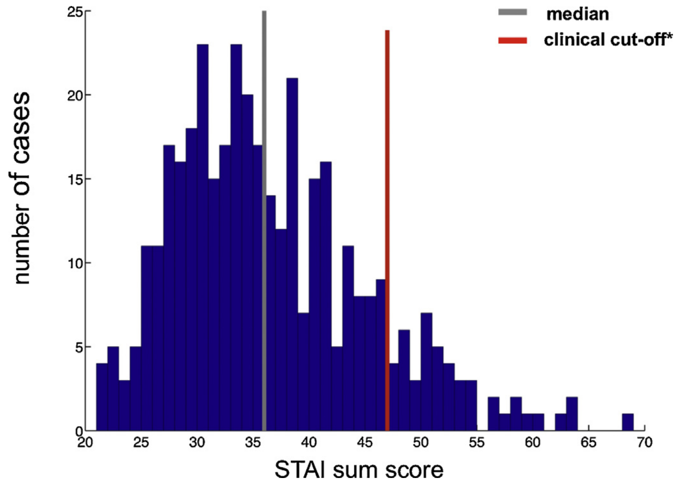

Fig. 1. Histogram depicting the distribution of STAI scores in the sample of 377 individuals as well as the median and an (empirical) clinical cut-off score. The distribution of STAI scores in our sample is similar to previous reports in college samples. The median in this sample corresponds to the score at which 52% of males and 42% of females of an average college student population score (http://psychology.ucdavis.edu/faculty_sites/sommerb/sommerdemo/stantests/norms.htm). * As the STAI is not a diagnostic tool, no obligatory clinical cut-off score is available. Typical scores for patients diagnosed with anxiety disorders are however in the range of 47 and above (Antony, Orsillo, & Roemer, 2001), which corresponds to 13% of females and 8% of males in our sample (in total ~10%).

information. Furthermore, the occurrence of dangerous (conditioning) and safe (extinction) contexts is not bound to different experimental days or phases (Gazendam et al., 2013), which would make them easy to discriminate based on temporal information, but it is implemented in an intertwined manner on each day. Hence, the paradigm is particularly suited to study context-dependent CS discrimination and thus promises to provide information above and beyond the existing literature.

We expected high trait anxiety to be associated with reduced ability to differentiate between potential threat and safe scenarios, potentially reflecting deficits in inhibitory learning to both conditioned cues and contexts.

2. Methods

2.1. Participants

In total, 377 individuals [116 males; age range 18–35, mean(s.e.m): 24.6(0.17); Spielberger Trait anxiety [STAI, Spielberger et al., 1983] sum score range: 21–69; STAI mean(s.e.m.): 37.1(0.44); see Fig. 1] involved in a large data collection comprised of different experimental tasks and different questionnaires on two consecutive days participated in the study (for further details on the sample and on data collection see supplementary material). All participants provided written informed consent and the study was approved by the local ethics committee (General Medical Council Hamburg).

2.2. Experimental paradigm

Versions similar to this paradigm have been described elsewhere (Haaker et al., 2013; Kalisch et al., 2006; Lonsdorf et al., in press). In brief, the experiment consisted of a context-dependent fear conditioning and extinction learning task (day 1) and recall/expression of fear and extinction memory (day 2, see Fig. 2). The experiment employed a within-subject A1B1A2B2 design consisting of two interleaved blocks (each block included 12 presentations of the CS+ and CS− for 3 s each; ITI duration 2.5–4 s) of uninstructed fear conditioning in context A and extinction in context B on day 1 (Learning). Two geometric symbols (circle and triangle) served as CSs presented on a blue or yellow screen background, which served as different contexts. Assignment of the geometric symbol and the CS-type was randomized and counterbalanced over participants, in the same manner as the assignment of the background color as the acquisition or extinction context. Thereby, the CS+ in context A was in 50% of the trials paired with the aversive, individually adjusted electrotactile US (onset 2.5 s after CS onset, train of 3 square-wave pulses of 2 ms), whereas the CS− was never paired with a US. The