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E. Glotzbach-Schoon[1] · M. Andreatta[1] · A. Mühlberger[2] · P. Pauli[1]
[1] Department of Psychology I, Biological Psychology, Clinical Psychology, and Psychotherapy, University of Würzburg, Würzburg
[2] Department of Clinical Psychology, and Psychotherapy, University of Regensburg, Regensburg

Context conditioning in virtual reality as a model for pathological anxiety

Anxiety and fear

With a 12-month prevalence of 14%, anxiety disorders belong to the most common psychological disorders. In phobias, fear is directed towards a specific object (e.g., specific animals, height) or situation (e.g., thunderstorm, darkness). Patients report strong fear when they are confronted with such stimuli. Contrastingly, patients with non-phobic anxiety disorders (e.g., panic disorder, posttraumatic stress disorder) report longer lasting diffused anxieties for which they cannot name a distinctly identifiable trigger. In lay terms, both are called anxiety. However, fear is scientifically defined differently from anxiety. *Fear* is related to a specific threat, whereas *anxiety* is triggered through a threatening context condition. Based on animal studies, Fanselow [15] postulated a "predatory imminence continuum", stating that the closeness to an imminent threat is decisive for defensive behavior. If the cues about the closeness of an enemy are unspecific (e.g., a dangerous area) and the threat has not yet been detected (*pre-encounter phase*), vigilance and careful behavior are manifested and constitute anxiety. If the threat has been detected (*post-encounter phase*) then freezing happens. If the aggressor is in close proximity or attacks, the behavior turns into fight or flight and constitutes *fear*. Anxiety, fear, and the accompanying behavior are probably controlled by different neuronal circuits ([13]; see Wotjak and Pape in this issue). These can be activated by phylogenetically relevant or associated stimuli [42].

Pathological fear or pathological anxiety is exhibited when no real threat is present or when the real threat cannot explain the strength and/or duration of the fear response. In addition, patients with anxiety disorders recognize the irrationality of their fears, suffer from the fear, and feel restricted by the fear in their professional and private lives ([56]; see Domschke in this issue). Perhaps, associative learning processes, especially conditioning, are decisive for the development of anxiety disorders [43]. Fear conditioning is an established model for the development of phobias (see Wotjak and Pape in this issue). In fear conditioning, a previously neutral stimulus, the conditioned stimulus (CS), becomes associated with an aversive stimulus, the unconditioned stimulus (US), due to a temporospatial contingency. After a few learning trials, the presentation of the CS is sufficient to provoke the fear reaction, i.e., the conditioned reaction (CR) [46]. As soon as the CS disappears, the fear reaction decreases. The absence of the CS signals safety because no aversive US is to be expected [50]. In other words, fear is triggered by a specific CS and this is referred to as *cue conditioning*. Lesion and imaging studies have identified the amygdala as the key brain structure for this kind of fear conditioning [6, 9, 32, 35].

Context conditioning, on the other hand, is a model for the development of

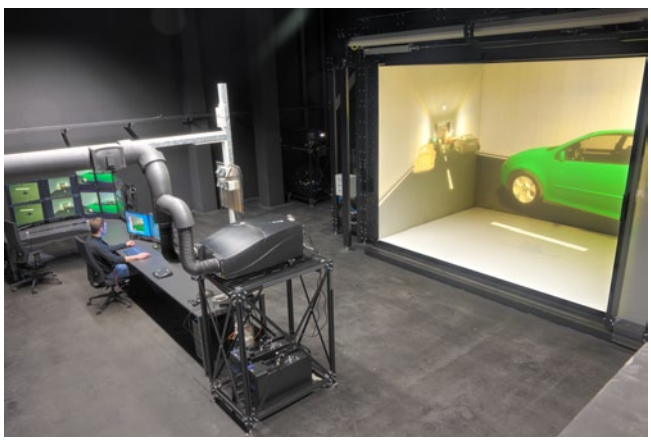

Fig. 1 ▲ The 3D multisensory cave automated virtual environment (*CAVE*) system of the Department of Psychology I at the University of Würzburg. The CAVE cube is closed and the virtual reality is projected from the outside on the four cube walls and the floor using five projectors so that the participant is completely surrounded by the virtual world. The participant's reactions and behavior in the virtual world can be recorded and later analyzed

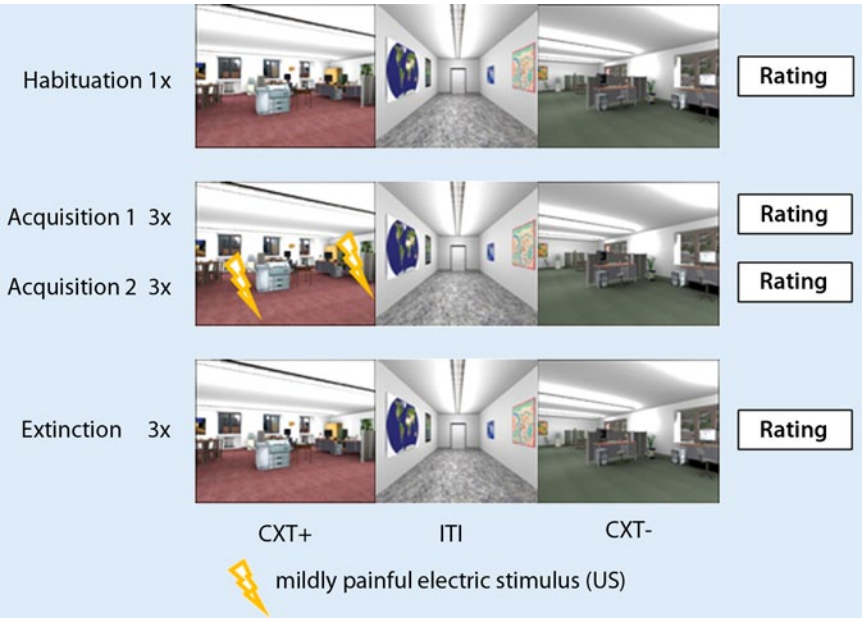

Fig. 2 ▲ Schematic representation of the conditioning paradigm. During a habituation phase participants are allowed to become familiar with the virtual rooms. In order to do so, they actively go into each room one at a time using a joystick. Subsequently, there are two acquisition phases. While a participant is in a virtual office, electric stimuli (unconditioned stimulus, US) are applied. Therefore, this room becomes the anxiety context (CXT+). In the second office, an electric stimulus is never administered. This room becomes the safety context (CXT–). The participants are led through the rooms on a predefined path. The order is always: first context, corridor, second context. This path is repeated three times for each acquisition phase and three times during the extinction. There are no electric stimuli in the extinction phase. Between each phase, ratings of the different contexts are recorded

longer-lasting anxiety [20]. Here, the US is presented unpredictably, i.e., independent of specific cue stimuli. Context is the best predictor of the US and becomes associated with the US [21, 54]. As the threat cannot be precisely predicted due to the lack of specific cue stimuli, there is no period of safety in this context. The individual has to permanently expect the US and, consequently, experiences chronic and long-lasting anxiety [49, 50]. Lesion and imaging studies have identified the amygdala, the intermediate core of the stria terminalis (bed nucleus stria terminalis, BNST), and the hippocampus as the important brain structures for this kind of conditioning ([1, 2, 13, 29]; see Wotjak and Pape in this issue).

Fear reactions to a conditioned cue or context decrease if the cue stimulus or context is presented repeatedly without the US. However, this so called *extinction* does not imply that the originally learned association is forgotten. In fact, animal and human studies have shown that the ventromedial prefrontal cortex inhibits the amygdala during extinction and, thus, fear and anxiety reactions are regulated ([28, 34, 40]; see Wotjak and Pape in this issue).

Context conditioning probably plays an important role in anxiety disorders which are characterized by longer-lasting stimulus-independent phases of anxiety. Therefore, the transfer of existing research paradigms from animal to human and clinical studies is an important step for the understanding of anxiety disorders. In animal studies, simple paradigms serve as context stimuli, for example, the immediate cage surroundings. An important aspect of this is that the animals are in the context and can explore the space [47]. The importance of the hippocampus for context conditioning underlines the role of a "spatial" representation of the context [45]. Therefore, to conduct this in a close analogy with humans it is necessary to enable spatial exploring of the context under controlled laboratory conditions. Virtual reality (VR) opens new possibilities for this (see **Excursus 1**, **Abb. 1**). Hereafter, we will give an overview of context conditioning studies which have been realized in VR.

Context conditioning in virtual reality

Context conditioning in VR was first realized by the workgroup of Christian Grillon (e.g., [4, 24]) and was further developed by our work group and others [17, 18, 53]. The research paradigms are based on virtual worlds, consisting of different contexts (e.g., offices, supermarkets, apartments), which are presented to participants using a HMD. The participants can enter and can also explore the virtual world most of the time. So far, the following paradigms have been realized in VR.

In *foreground context conditioning*, the US is applied unpredictably in a certain context either between cue stimuli (CS), which then do not predict the US (CS–US unpaired), or without a specific cue stimulus (US only). In both cases, the context is the best predictor of the US. In animal models, these two research paradigms (CS–US unpaired versus US only) do not differ in the strength of the conditioned fear reaction [38].

Background context conditioning has also been studied using VR. Here, the US is predictable through a cue stimulus (CS–US paired), but the influence of the background context on the cue conditioning is being studied [3, 4, 5]. For example, these studies showed that fear increases in a context if the contingency between cue and US has not been explicitly learned [5]. Grillon et al. [24] and Alvarez et al. [2] mostly compared a context in which the US was not predictable (CS–US unpaired) to a context in which the US was predicable (CS–US paired). Grillon et al. [24] showed that the context in which the US was unpredictable triggered a stronger fear reaction and avoidance behavior than the context in which the US was predictable.

Our VR-based context conditioning paradigm for human experiments was developed analogous to the US-only studies (see **Excursus 2** for a more detailed description of the experimental design). The participants found themselves in a virtual world consisting of two offices (contexts) which could be entered via a

Excursus 1 Virtual reality as a tool for experimental emotion research

Virtual reality (VR) is a form of human-computer interaction, in which humans are not only observers of a screen presentation but an active part of a computer-generated three-dimensional world. The user can move in the VR, receive feedback about his or her activities and, if necessary, interact with the presented environment and other users. The goal is to achieve a maximum of immersion (covering of the senses with virtual sensual impressions) and feeling of presence (subjective feeling of diving into the virtual environment) in the VR. The three-dimensional virtual environment can be realized using different displays as well as input and output devices. The two most important presentation systems are head mounted displays (HMDs, see **Fig. 4a**) and walk in VR interfaces (cave automated virtual environment, CAVE; see **Fig. 1**).

Current systems mostly work with visual and auditory simulations. In addition, there are also systems that convey olfactory, haptic, and vestibular information. The choice of the components depends on the research question and on the available resources. For example, it seems that the use of movement platforms is useful for inducing emotions for movement-related fears (e.g., aviophobia). Nowadays, VR is successfully used in clinical research and therapy of anxiety disorders. Exposure therapy (see Wotjak and Pape, this issue) in VR (virtual reality exposure therapy, VRET) is an effective alternative to in vivo exposure therapy (see [39, 44]) because in vivo exposure therapy is time- and cost-intensive and therefore used seldom. VR is also successfully used in social psychology [7] as well as clinical basic research and experimental emotion research (see [4, 18]; or this article). The most important advantages of VR for experimental emotion research are the following:

- the environment can be completely controlled,
- participants experience VR as a space they can actively explore,
- specific emotion triggers (e.g., fear stimuli) can be realized on demand and can be repeated as often as required,
- the reactions of the participants can be observed and recorded precisely,
- VR is an interesting research environment for participants, especially for children,
- lower costs and less organizational efforts than field studies and other laboratory spaces, and
- it is possible to trigger emotions closer to reality than in traditional laboratory paradigms.

corridor (**Fig. 2**). One of the offices became the anxiety context (CXT+) where unpredictable and slightly painful electric stimuli (US) were applied to the participants. The second room became the safety context (CXT–) where the participants never experienced electric stimuli. The VR paradigm allowed recording of fear reactions on three levels: The *explicit verbal level* (ratings for valence, arousal, and anxiety), the *behavioral level* (approach and avoidance), and the *physiological level* (startle reflex, skin conductance).

The explicit verbal level

As expected, the success of VR context conditioning was represented in the anxiety ratings of the participants. It was found throughout all our studies that the virtual anxiety context, compared to the safety context, elicits stronger anxiety (see **Fig. 3a**) and is rated with a negative valence and as arousing in the course of the conditioning. Interestingly, the heightened anxiety is observable in the anxiety context even after the extinction which indicated a slow extinction process. The increased contingency ratings between context and US confirm that the participants expect the US more in the anxiety context than in the safety context [17, 18, 53].

The behavioral level

In order to test whether context conditioning has an influence on participants' behavior, we studied their approach and avoidance behavior [17]. Immediately after the conditioning phase, participants could choose which virtual room they wanted to enter once more: The anxiety context, the safety context, or a neutral context, consisting of a third office, which the participants knew about but which was irrelevant for the learning phases. The participants could only enter two of the three contexts consecutively and, thus, had to avoid one of the contexts. Most of the participants (~65%) did not want to enter the anxiety context once more. Interestingly, we found evidence that this avoidance behavior is decisively dependent on the strength of the context conditioning (defined as the difference between reported anxiety in the anxiety context versus the safety context). Participants who avoided the anxiety context experienced particularly high anxiety after the learning trials (**Fig. 3b**, left bar). This does not apply to participants who avoided the safety context after the learning trials (**Fig. 3b**, right bar) and so it can be assumed that there was no context conditioning in these participants. These results indicate that the explicit conscious rating of the anxiety context is decisive for later avoidance behavior. Future studies shall test whether this is accompanied by increased vulnerability for anxiety disorders.

Abstract

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Context conditioning in virtual reality as a model for pathological anxiety

Abstract

Phobic fear which is triggered by specific stimuli can be modeled experimentally through cue conditioning. In contrast, context conditioning may serve as a model for anxiety which is longer lasting and unrelated to cues. Such context conditioning can be studied in humans in analogy to animal studies by using virtual reality (VR). Our VR context conditioning paradigm uses virtual offices as contexts. One office becomes the anxiety context since participants receive unpredictable mildly painful electric stimulations. The other office becomes the safety context because no aversive stimulation is delivered while participants explore this office. The validity of the paradigm is indicated in the findings that after conditioning participants rate the virtual anxiety context as anxiety eliciting, avoid this context, and show startle potentiation in this context. Our studies further revealed that known risk factors for anxiety disorders affect context conditioning. We found that enhanced trait anxiety facilitates contextual fear conditioning. In addition, we observed that individuals with genetic risks for anxiety disorders learn context conditioning very effectively as shown in startle potentiation. These findings suggest that in individuals vulnerable to anxiety disorders such as panic disorder or posttraumatic stress disorder, context conditioning may have contributed to the development of these disorders.

Keywords

Fear · Anxiety · Conditioning · Virtual reality

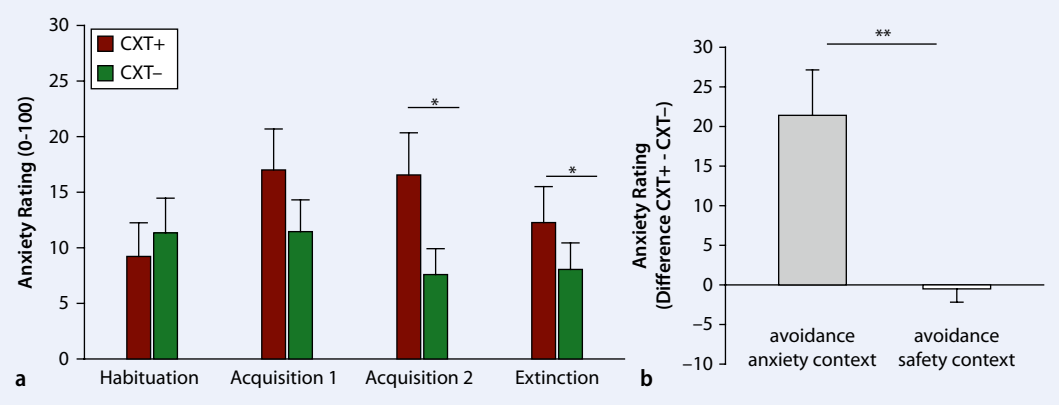

Fig. 3 ▲ Anxiety ratings after the different phases of the experiment (**a**) and depending on avoidance behavior after acquisition (**b**). **a** Anxiety ratings are not different for the contexts after habituation and the first acquisition phase. However, after the second acquisition phase the anxiety context (CXT+) is rated with higher anxiety than the safety context (CXT–). This difference is still present after the extinction. **b** Participants who avoid the anxiety context during acquisition (*left bar*) show a stronger context conditioning effect (difference between CXT+ and CXT–) than participants who avoid the safety context (*right bar*). Therefore, it seems that subjectively experienced anxiety has a decisive role for avoidance behavior. In both **a** and **b**, means and standard errors are depicted. *p<0.05, **p<0.01

Excursus 2 The VR paradigm

The virtual worlds are typically presented via a HMD and consist of different contexts, for example, two different offices which can be entered via a corridor (**Fig. 2**). In some phases of the study, the participants can explore the virtual world by navigating themselves using a joystick. In other phases, the participants are moved through the virtual world on a predefined path. The head movements of the participants are always recorded and the field of view is always adapted to the head movements so that the participants can look around in the VR environment, just like in a real room.

First, all participants complete a habituation phase in all studies, in which they can explore the VR environment freely. This is followed by two learning phases (Acquisition 1 and 2) where the participants are presented thrice per phase in one of the contexts in a pseudorandomized order. During these acquisition phases in one room (anxiety context, CXT+), the US is unpredictably administered three times. In contrast, the US is never administered in any other office (safety context, CXT–). During the final test or extinction phase, the participants go into the two rooms again but the US is no longer presented (see Wotjak and Pape, this issue). After each acquisition and extinction phase, valence, arousal, anxiety, and contingency of the contexts are rated, and the physiological parameters (startle response and skin conductance) are recorded.

Excursus 3 The fear-potentiated startle response

The startle response is a defensive reflex which protects from injuries and shortens the latency of defensive actions [16, 30]. The startle response can be triggered by sudden intensive stimuli. The acoustic startle reflex, for example, is triggered by a sudden, loud acoustic stimulus. This stimulus is processed in the nucleus reticularis pontis caudalis (NRPc) of the brainstem and triggers extremely fast muscle contractions via efferent projections to motor neurons. Animal studies have shown that the amplitude of the startle response is modulated by the emotional–motivational state of the organism. Successful fear conditioning, for example, is represented by potentiated amplitude of the startle response in presence of the conditioned cue stimulus (CS). This effect is conveyed by the influence of the central nucleus of the amygdala on the NRPc [30]. In addition, appetitive stimuli also modulate the startle response, probably via afferent projections from the nucleus accumbens to the NRPc [30]. The potentiated startle response in humans is an implicit, non-verbal indicator of fear and anxiety. In human studies, usually short and very loud (50 ms, 95–105 db) white noise is presented via head phones (**Fig. 4a**), and the contraction of the orbicularis oculi muscle, which runs around the eye and controls the eye lid closing, is measured [8]. **Fig. 4a** shows the position of the electrodes below the eye. The electric activity of the muscle is registered, the raw signals are integrated (**Fig. 4b**), and from this the amplitude of the startle response is determined (typically 20–120 ms after stimulation; **Fig. 4d**). The affect modulation is represented, for example, in the potentiation of the amplitude when negative-valence pictures are presented or in a decrease when positive images are presented, as compared to neutral images, respectively (**Fig. 4c**; [33]).

The physiological level

As a physiological indicator of fear and anxiety in human studies, the fear-potentiated startle response is particularly interesting, as this parameter is often measured in animal studies and, thus, an immediate reference to such studies is possible (see **Excursus 3**).

We presented startle stimuli repeatedly via headphones in different contexts in order to measure startle response as a physiological indicator of anxiety [53]. The tonic skin conductance, as a physiological measure of arousal, was analyzed especially between entering and exiting the virtual contexts. The continuous decline in the strength of the startle response observed during the course of our study (**Fig. 5**) is typical for human studies and can be attributed to unspecific habituation processes. It is important for context conditioning that there are no differences prior to conditioning (habituation phase) and that significant differences between anxiety and safety context develop during conditioning. These effects were found in the last acquisition phase, as depicted in **Fig. 5**. The startle response was potentiated in the anxiety context as compared to the safety context and this difference again disappeared after the extinction phase. This process is typical for successful fear conditioning and was found in our studies with a similar pattern for the

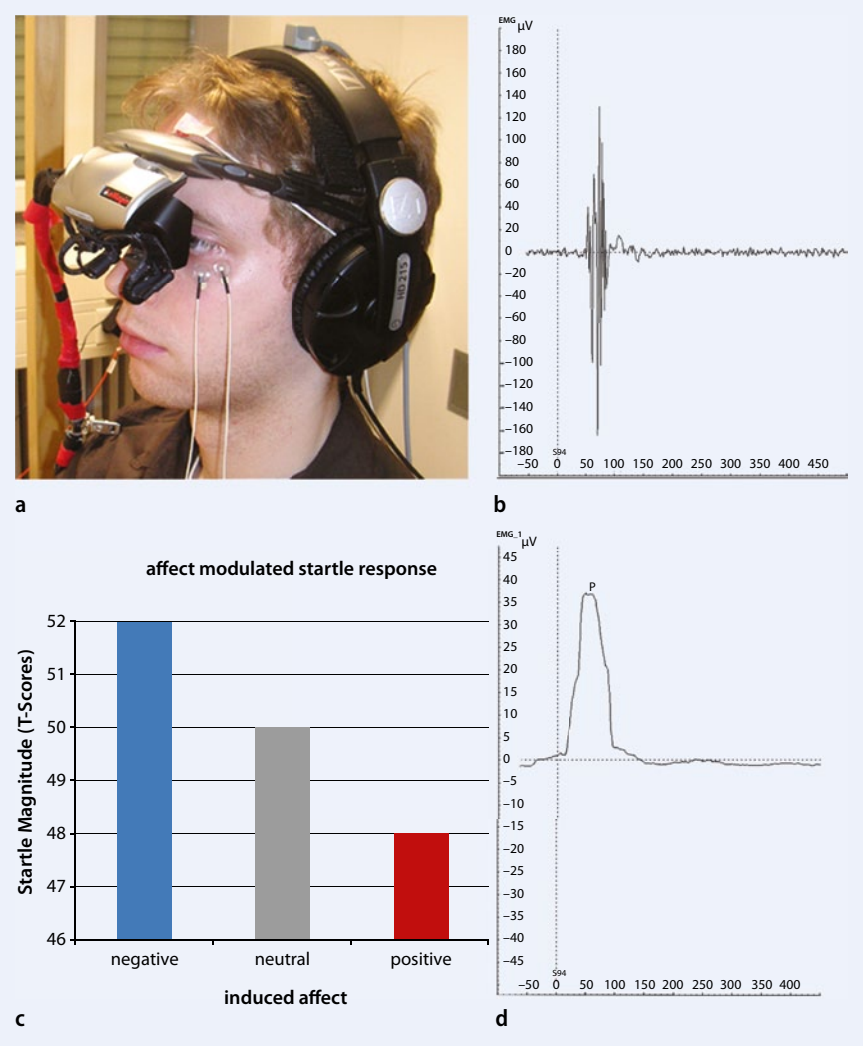

Fig. 4 ▲ Measuring the startle response in humans. **a** The virtual world is presented via a head mounted display and the startle stimulus is played back via headphones. **b** At the same time the contraction of the orbicularis oculi muscle below the eye is recorded. **d** This is integrated in further processing steps, so that the amplitude of the startle response can be measured (in µV), which appears about 20–120 ms after the startle sound. **c** Compared to neutral images, the affect modulation of the startle response is either potentiated during negative images or reduced when positive images are presented compared to neutral images

tonic skin conductance as an indicator of anxious arousal [18, 53].

Interindividual differences in context conditioning

Because context conditioning is a model for longer lasting states of anxiety, a quicker and stronger context conditioning could be a risk factor for the development of anxiety disorders. Therefore, it is of particular importance to identify individual variables, namely personality traits and genetic factors, which are associated with this risk factor.

Trait anxiety seems to be a general risk factor for the development of anxiety disorders [10, 41]. Here, trait anxiety is defined as a general tendency to rate situations as threatening and, thus, to experience a higher level of *state anxiety* as well [51]. Hence, one can speculate that increased trait anxiety facilitates context conditioning. In order to test this hypothesis, we studied selected participants with pronounced and reduced trait anxiety in our VR context conditioning paradigm [18]. We found that high trait-anxious participants acquired context conditioning faster than low trait-anxious participants (**Fig. 6**). Further studies hint in a similar direction. High trait-anxious individuals are worse at regulating their anxiety in a threatening context [3] and this seems to be associated with a lower activation in the prefrontal cortex [27]. Given these findings, it stands to reason that high trait anxiety is a risk factor for the development of anxiety disorders based on context conditioning.

In recent years, genetic polymorphisms have been specially discussed as risk factors for anxiety. A polymorphism in the promoter region (5-HTTLPR) of the serotonin transporter gene (*SLC6A4*; see Sachser and Lesch in this issue) is the most studied genotype in relation to anxiety. The *S* allele has been associated with posttraumatic stress disorder (PTSD; [31, 55]) and increased anxiety [36, 48]. Furthermore, individuals with the S allele show higher amygdala activation to emotional stimuli [11, 25] and a stronger fear-potentiated startle response to a conditioned cue stimulus [37] compared to homozygotic L allele carriers. More recent studies have shown a relation between panic disorder and the T allele of neuropeptide S (NPS) receptor gene (*NPSR1*; rs324981; [14]). In addition, fear relevant stimuli (fearful faces) trigger stronger amygdala activation in healthy T allele carriers compared to A allele carriers [12]. The S allele of the 5-HTTLPR polymorphism and the T allele of *NPSR1,* thus, seem to be risk alleles for anxiety disorders.

Using our VR context conditioning paradigm, we studied if the S allele and the T allele carriers are also characterized by a stronger context conditioning since faster and stronger context conditioning may add to the development of anxiety disorders. Here, we found that context conditioning is influenced by an interaction of the two genotypes on a physiological level [19]. Only carriers of both risk alleles (S and T allele) showed a higher startle response in the anxiety context in comparison to the safety context. Moreover, recent evidence suggests that contextual anxiety could also be modulated by a polymorphism in the promoter region of the cannabinoid receptor gene (*CNR1*, rs2180619), a risk gene for anxiety disorders. There are no studies on context con-

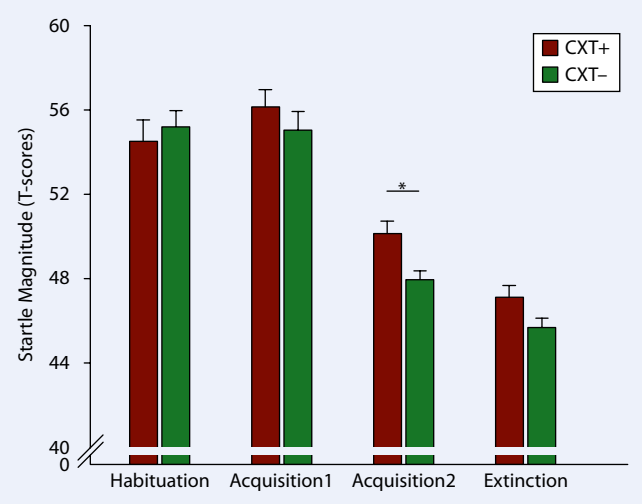

Fig. 5 ▲ Fear-potentiated startle response in a context conditioning paradigm. During habituation, there are no visible differences between the conditions. A differential conditioning effect is only shown in Acquisition phase 2. The potentiation of the startle response is higher in the anxiety context than in the safety context. This difference is no longer significant after the extinction phase. Means and standard errors are depicted. *p<0.05, **p<0.01, ***p<0.001

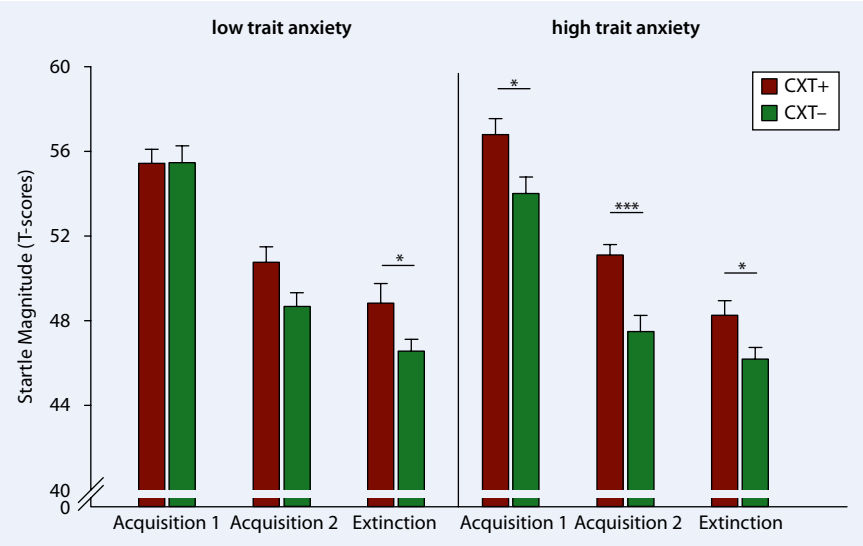

Fig. 6 ▲ Fear-potentiated startle response in low-anxious (*left*) and high-anxious (*right*) participants. Highly anxious participants already show a higher potentiation in the first acquisition phase in the anxiety context (CXT+) compared to the safety context (CXT–), whereas this difference is only present in the extinction phase in low anxiety participants. Means and standard errors are depicted. *p<0.05, **p<0.01, ***p<0.001

ditioning about this polymorphism so far but homozygotic A allele carriers have shown deficits in extinction of cue conditioning which has been associated with a higher fear reaction to the background context [26]. These data suggest that genetic polymorphisms—which are associated with an increased risk for anxiety disorders—either facilitate context conditioning or are characterized by an extinction deficit leading to increased contextual anxiety.

Summary and outlook

VR is a computer-generated environment, which allows the user to immerse in a virtual world and to experience this world. This approach opens new possibilities for neuroscience research, especially behavioral neuroscience in animals and humans (compare [52]). With regard to fear, anxiety, and anxiety disorders (the topics of SFB-TRR 58), VR has so far been mostly studied as a novel form of therapy (VRET; compare [44]). Lately, it has also become an instrument for basic research (compare [24]).

Context conditioning probably plays a decisive role in the development of longer lasting chronic states of anxiety and, thus, for anxiety disorders [13]. The usefulness of VR to study context conditioning in humans is self-evident. Our studies confirmed the validity of a VR context conditioning paradigm and showed that the virtual context associated with slightly aversive pain stimuli triggered fear reactions on the explicit verbal (ratings), the implicit biological (potentiated startle response), and behavioral level. In addition, our follow-up studies could show that risk factors for anxiety disorders (i.e., increased trait anxiety and genetic polymorphisms for panic disorder and PTSD) facilitated context conditioning. Thus, one may speculate that context stimuli in high-risk individuals become fear stimuli particularly quickly and effectively, which then trigger longer-lasting chronic states of anxiety and via this path support the development of anxiety disorders.

Future research can now use VR to further study context conditioning in humans. On the one hand, studies with patient groups are interesting for testing the hypothesis that panic and PTSD patients learn context conditioning particularly easily (also see [22, 23]) and have difficulties in its extinction. Here, the question would also be whether patients have a deficit in cognitively controlling anxiety that has been acquired through context conditioning based on frontal brain activity. On the other hand, VR, which can be selectively and specifically manipulated, can be used ideally to test which characteristics of a context

are important for context conditioning. Are these distinct characteristics of the context or are the cognitive–spatial representations important? Which context characteristics are important for generalization and extinction processes? Answering these questions will also be important for optimizing the treatment of anxiety disorders.

Corresponding address

E. Glotzbach-Schoon
Department of Psychology I, Biological Psychology, Clinical Psychology, and Psychotherapy, University of Würzburg
Marcusstr. 9–11, 97070 Würzburg
Germany
evelyn.glotzbach@psychologie.uni-wuerzburg.de

E. Glotzbach-Schoon. Evelyn Glotzbach-Schoon is a PhD student in the Collaborative Research Centres (German: Sonderforschungsbereich, SFB) "Fear, Anxiety, and Anxiety Disorders" (SFB TRR 58) in subproject B01 with Prof. Dr. Paul Pauli and Prof. Dr. Andreas Mühlberger. She studied psychology at the University of Würzburg from 2003–2008.

Corresponding address

Dr. M. Andreatta
Department of Psychology I, Biological Psychology, Clinical Psychology, and Psychotherapy, University of Würzburg
Marcusstr. 9–11, 97070 Würzburg
Germany
marta.andreatta@mail.uni-wuerzburg.de

M. Andreatta. Dr. Marta Andreatta is a postdoctoral fellow in the work group "Biological Psychology, Clinical Psychology, and Psychotherapy" of Prof. Dr. Paul Pauli. She studied psychology at the University of Padua (Italy) and acquired a doctoral degree in 2010 about associative learning in the Co-Tutela procedure at the University of Würzburg (Prof. Dr. P. Pauli) and University of Padua (Prof. Dr. A. Angrilli).

Corresponding address

Prof. Dr. A. Mühlberger
Department of Clinical Psychology, and Psychotherapy, University of Regensburg
Universitätsstr. 31, 93053 Regensburg
Germany
andreas.muehlberger@ur.de

A. Mühlberger. Prof. Dr. Andreas Mühlberger is head of the newly founded Department of Clinical Psychology and Psychotherapy at the University of Regensburg since 2012. He studied psychology and psychotherapy at the University of Würzburg and acquired a PhD at the Graduate School of Neurobiology, University of Tübingen. He returned to Würzburg in 2001 and finished his habilitation in 2007 at the Department of Biological Psychology, Clinical Psychology, and Psychotherapy. His research focus is the development and treatment of anxiety disorders, especially using virtual reality. This comprises basic research questions, for example the study of interindividual differences in context conditioning, and applied questions, for example the evaluation and optimization of psychotherapeutic interventions.

Corresponding address

Prof. Dr. P. Pauli
Department of Psychology I, Biological Psychology, Clinical Psychology, and Psychotherapy, University of Würzburg
Marcusstr. 9–11, 97070 Würzburg
Germany
pauli@psychologie.uni-wuerzburg.de

P. Pauli. Prof. Dr. Paul Pauli is head of the Department of Biological Psychology, Clinical Psychology, and Psychotherapy at the University of Würzburg since 2001. He studied psychology at the University of Tübingen and received a research stipend at the Max Planck Institute of Psychiatry in Munich after that. After receiving his PhD in 1991, he became associate and then senior associate scientist with Prof. Birbaumer at the University of Tübingen, where he habilitated in 1997. In 2000, he became the Chair of Clinical Psychology Research at the University of Southampton, England. He is the speaker of the DFG Graduate School RTG 1253 "Processing of affective stimuli: from the molecular basis to the emotional experience", vice speaker of the Section of Neuroscience of the Graduate School of Life Sciences at the University of Würzburg, and DFG-Liaison officer at the University of Würzburg.

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Compliance with ethical guidelines

Conflict of interest. E. Glotzbach-Schoon, M. Andreatta, A. Mühlberger, and P. Pauli state that there are no conflicts of interest.

All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies.

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