Journal of Anxiety Disorders 44 (2016) 36–46

Contents lists available at ScienceDirect

Journal of Anxiety Disorders

Fear conditioning and stimulus generalization in patients with social anxiety disorder

Lea M. Ahrens[a,*], Paul Pauli[a,b], Andreas Reif[c], Andreas Mühlberger[d], Gernot Langs[e], Tim Aalderink[e], Matthias J. Wieser[a,f]

[a] Department of Psychology I, University of Würzburg, Germany
[b] Center of Mental Health, Medical Faculty, University of Würzburg, Germany
[c] Department of Psychiatry, Psychosomatics and Psychotherapy, University of Frankfurt, Germany
[d] Department of Psychology (Clinical Psychology and Psychotherapy), University of Regensburg, Germany
[e] Schön Klinik Bad Bramstedt, Germany
[f] Institute of Psychology, Erasmus University Rotterdam, Netherlands

ARTICLE INFO

Article history:
Received 18 December 2015
Received in revised form 4 August 2016
Accepted 4 October 2016
Available online 5 October 2016

Keywords:
Fear conditioning
Fear generalization
Social anxiety disorder
Patients
Heart rate
Skin conductance response

ABSTRACT

Although overgeneralization seems to be a hallmark of several anxiety disorders, this until now has not been investigated in social anxiety disorder (SAD). Therefore, we examined fear generalization in 26 SAD patients and 29 healthy controls (HC) using two faces as conditioned stimuli (CS+, CS−), and a loud scream and a fearful face as unconditioned stimulus (US). Generalization was tested by presenting both CS and four morphs of the two faces (generalization stimuli [GSs]), while ratings, heart rate (HR) and skin conductance responses (SCR) were recorded. Results revealed that SAD patients rated all stimuli as less pleasant and more arousing compared to HC. Moreover, ratings and SCR indicated that both groups generalized their acquired fear from the CS+ to GSs. Remarkably, only SAD patients showed generalization in HR responses (fear bradycardia). Overall, SAD seems not to be characterized by strong overgeneralization but discrepancies in fear responses to both conditioned and generalized threat stimuli.

1. Introduction

While fear usually is a very adaptive emotion which allows us to react to immediate threat and helps us to foresee dangerous situations in the future, it can become pathological if the fear is excessive or unreasonable and significantly interferes with a person's daily routine (LeDoux, 2003). Many etiological approaches to the study of anxiety disorders suggest classical fear conditioning – the process through which a neutral conditioned stimulus (CS) acquires the ability to elicit fear following its co-occurrence with an aversive unconditioned stimulus (US) (Pavlov, 1927) – to be a good translational model of the acquisition of clinically relevant fear (Mineka & Zinbarg, 2006). Researchers have tried to identify at which point patients with anxiety disorders deviate from healthy controls (HC) in fear learning processes and consider enhanced acquisition, resistance to extinction, inhibition deficits and overgeneralization of conditioned fear as possible factors (e.g. Briscione, Jovanovic, & Norrholm, 2014; Duits et al., 2015; Lissek et al., 2005).

Fear learning is rarely limited to the specific US-CS combination that is conditioned in the first place, but can be broadened to both stimuli (stimulus generalization) and situations (context generalization) that are qualitatively similar to the original association cues (CSs) (for reviews, see Bouton, 2004; Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2014). This is – to a certain degree – reasonable, because potentially threatening stimuli usually do not occur in the exact same form at multiple encounters. For example, if a person gets bitten by a dog, he or she might avoid other dogs in the future, too, because he or she anticipates that they might bite as well (stimulus generalization). Also, it is possible that another person who gets robbed in a specific park at night afterwards avoids parks in general at night-time (context generalization; see Andreatta, Leombruni, Glotzbach-Schoon, Pauli, & Mühlberger, 2015). Therefore, especially in case of fear relative to other emotions, namely when a stimulus predicts an aversive outcome, it is prudent to show wider generalization, because a miss is more costly than a false alarm (Dunsmoor & Paz, 2015). Likewise, it

* Corresponding author at: University of Würzburg, Department of Psychology, Biological Psychology, Clinical Psychology, and Psychotherapy, Marcusstr. 9-11, D-97070 Würzburg, Germany.
E-mail address: lea.ahrens@uni-wuerzburg.de (L.M. Ahrens).

http://dx.doi.org/10.1016/j.janxdis.2016.10.003
0887-6185/

is essential to discriminate among different stimuli in order to conserve resources and diminish redundant fight-or-flight reactions or avoidance behavior when there is no threat. However, several studies found that the ability of patients with anxiety disorders to differentiate among danger and safety signals is diminished (for a recent meta-analysis, see Duits et al., 2015). Without this ability, it is likely that these patients have a predisposition to show stronger generalization than healthy people, as seen for example in PTSD. A recent study showed that patients with PTSD overgeneralize their conditioned fear reaction from the original CS to other stimuli which share its physical features compared to controls (Lissek & Grillon, 2012). As a consequence, one might conclude that patients suffering from trauma do not only experience symptoms when they are confronted with the original stimulus which caused the PTSD, but also when they are exposed to traumatic reminders or trauma-related stimuli. These might be sufficient to trigger a stress reaction including intrusive symptoms, avoidance of trauma-related reminders (e.g., people, places, conversations, activities, objects, or situations) and alterations in arousal and reactivity (e.g. hypervigilance) (see DSM-V, American Psychiatric Association, 2013). Thus, overgeneralization, in particular, might be a promising candidate to help explain pathological anxiety and the fear-related symptoms of trauma- and stressor-related disorders, such as PTSD and specific phobias (Dymond, Dunsmoor et al., 2014).

The phenomenon of fear generalization, in which a conditioned fear response spreads to related stimuli, has been explored in animals (e.g. Hull, 1943; Pavlov, 1927) and humans (Bass & Hull, 1934; Hovland, 1937) for almost a century. However, as this field of research has then been neglected for several decades after the initial interest, surprisingly little is known about fear generalization, especially in clinical populations. During the last years, researchers gained new interest in stimulus generalization and tested generalization paradigms in both healthy individuals (e.g. Lissek, Biggs et al., 2008; Norrholm et al., 2014; Vervliet, Vansteenwegen, & Eelen, 2004) and patients with anxiety disorders (for a review, see Dymond, Dunsmoor et al., 2014). So far, the data revealed overgeneralization of fear in panic disorder (PD) (Lissek et al., 2010; Lissek, 2012) and, as mentioned above, post-traumatic stress disorder (PTSD) (Lissek & Grillon, 2012). In other words, patients did not show fear responses only to the danger (CS+), but also to generalization stimuli (GSs), which are qualitatively different intermediate stimuli between CS+ and CS−. These studies also revealed that the generalization gradients of HC follow quadratic trends, whereas anxiety patients showed linear declines.

Interestingly, a recent study compared fear generalization between healthy adults and children and found that children – similar to anxiety patients – displayed heightened fear generalization in both explicit (arousal ratings) and implicit (skin conductance response) measures (Schiele et al., 2016). The authors suppose that enhanced fear generalization in children might be related to the insufficient maturation of brain structures responsible for the discrimination among danger and safety cues such as the prefrontal cortex. In a similar vein, the question arises whether the functioning of the same structures is impaired in anxiety patients. Further studies on psychiatrically healthy controls with low and high spider-fearfulness (Dymond, Schlund, Roche, & Whelan, 2014) or with low and high characteristics of obsessive-compulsive disorder (OCD), such as washing, obsessing, hoarding, ordering, checking and neutralizing, indicated by elevated scores on the Obsessive-Compulsive Inventory-Revised (OCI-R) (Kaczkurkin & Lissek, 2013), also found that these individuals overgeneralized their fear compared to controls. These outcomes, however, still have to be confirmed by studies testing clinical populations. With regard to generalized anxiety disorder (GAD), one study confirmed the aforementioned conclusions (Lissek et al., 2014), while others failed to detect overgeneralization in behavioral or psychophysiological responses (Greenberg, Carlson, Cha, Hajcak, & Mujica-Parodi, 2013; Tinoco-González et al., 2015). Consistent with these mixed results, another investigation with a sample of high trait anxious students observed no overgeneralization compared to low trait anxious students (Torrents-Rodas et al., 2012). In sum, results are contradictory, which is why the role of overgeneralization as a marker for anxiety disorders has not yet been fully clarified.

On a neuronal level, there are only a few studies on fear generalization to date, but a preliminary understanding of involved brain circuits has begun to emerge. In humans, the first fMRI study on fear generalization (Dunsmoor, Prince, Murty, Kragel, & LaBar, 2011) using moderately fearful faces (CS+) paired with shocks (US) compared with neutral faces (CS−) found generalized enhancement of activity to stimuli which were similar to the CS+ within regions involved in the acquisition and expression of conditioned fear, such as the thalamus, insula and caudate. On the contrary, participants displayed generalized neural activity to stimuli approximating the CS− in the ventromedial prefrontal cortex (vmPFC). Further studies found similar results, including positive generalization gradients – indicated by a decrease in activity as the presented stimulus differs from the CS+ – in the dorsomedial prefrontal cortex (dmPFC), caudate, insula, anterior cingulate cortex (ACC), right supplementary motor area (SMA), as well as, negative gradients in the hippocampus and vmPFC (Greenberg et al., 2013; Lissek et al., 2013).

With regard to anxiety disorders, there is only one fMRI study investigating generalization processes in GAD patients and the authors reported a “flat”, less discriminant vmPFC response slope in the GAD group, while healthy participants showed enhanced activity to GSs that resembled the CS− (Greenberg et al., 2013). This impairment to recruit the vmPFC by safety signals is hypothesized to be associated with wider fear generalization (Dunsmoor & Paz, 2015). Altogether, these findings indicate that fear generalization engages similar neural areas involved in the acquisition and regulation of conditioned fear (Dymond, Dunsmoor et al., 2014). A summary of the results by Lissek and colleagues led to a neurobiological model of fear generalization which comprises a network of brain areas including the hippocampus with connections to sensory cortices and brain areas associated with fear inhibition (vmPFC) and fear excitation (e.g. insula, ACC and amygdala) (Lissek et al., 2013; Lissek, 2012). According to this model, the exposure to GSs simultaneously spreads sensory information via two pathways proposed by LeDoux (LeDoux, 1998): a ‘quick and dirty’ route leading directly to the amygdala, which immediately initiates a conditioned fear response, and a ‘slow but elaborated’ route via the thalamus and visual cortices, which compares the new information of the GSs to the previously encoded CS+ through schematic matching. If there is a large overlap, the hippocampus reactivates the neural representation of the CS+ through pattern completion (Treves & Rolls, 1994) and thereby evokes a conditioned fear response. In contrast, insufficient overlap leads to the initiation of pattern separation (McHugh et al., 2007), which activates structures associated with fear inhibition, which in turn decrease the activity in the amygdala. However, a recent fMRI study using a circular fear-generalization paradigm with visual, circular cues, did not report a typical generalization gradient in all areas. Rather, the authors observed a high pattern-similarity between the CS+ and the US in the insula encoding the aversive quality of the CS+, and activity related to ambiguity-based outcome uncertainty indicated by differentiating intermediate stimuli from both the CS+ and CS− in the inferior temporal cortex (Onat & Büchel, 2015). These authors concluded that stimulus generalization is not only passively driven by perceptual similarity, but an active process which integrates activity from different areas related to threat identification and outcome uncertainty, and which can actively widen the scope of threat to perceptually similar stimuli.