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Functional neuroimaging of associative learning and generalization in specific phobia

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ABSTRACT

Background: Theoretical models have implicated classical fear conditioning, fear generalization, and extinction learning in the development of anxiety disorders. To date, it is largely unknown to what extent these mechanisms and the underlying neurobiology may be altered in specific phobia, a disorder characterized by focal fears. The current study systematically examined fear conditioning, fear generalization, extinction learning, and extinction recall in a sample of individuals with a specific phobia.

Methods: Participants with a specific phobia (SP) of spiders (n = 46) and healthy controls (HC) (n = 48) underwent a 3-day fMRI cue-conditioning protocol, including a fear acquisition and a fear generalization phase (day 1), an extinction learning phase (day 2), and an extinction recall phase (day 3). Stimuli were phobia-irrelevant, as geometrical shapes served as conditioned threat (CS+) and safety stimuli (CS-), and an electrical shock as the unconditioned stimulus (US). Self-reported fear, US expectancy, and blood-oxygen-level dependent responses were measured.

Results: Behavioral results only revealed enhanced CS+/CS-differentiation in fear scores during acquisition retention in SP. Some neural differences were observed during other task phases. During early fear acquisition, SP showed enhanced differential activation in the angular gyrus and lateral occipital cortex, and during extinction recall, more precuneus deactivation was found in SP compared to HC. There were no clear indications of altered neural fear generalization or extinction learning mechanisms in the SP group.

Conclusions: Results indicate that spider phobia may be characterized by enhanced differential fear retention and altered brain activation patterns during fear acquisition and extinction recall. The findings provide insight into the nature of fear learning alterations in specific phobia, and how these may differ from those found in disorders characterized by broad anxious distress.

1. Introduction

Anxiety disorders are characterized by excessive fear and/or anxiety and accompanying defensive states such as escape and avoidance behaviors (Association AP, 2013). Theoretical models have implicated alterations in fear acquisition, fear generalization, extinction learning, and extinction recall in the etiology of anxiety disorders (Duits et al., 2015; VanElzakker et al., 2014; Dymond et al., 2015). Laboratory studies have mostly provided evidence for alterations in these processes in individuals with high trait anxiety, and in those suffering from generalized anxiety disorder (GAD) or post-traumatic stress-disorder (PTSD) (Duits et al., 2015; Kaczkurkin et al., 2016; Lissek et al., 2014). Nevertheless, there is a shortcoming of studies looking at these processes in specific phobia.

The acquisition of clinically relevant fears has previously been modeled by fear conditioning or fear learning, a process by which a

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neutral conditioned stimulus (CS+) acquires the ability to elicit fear responses by its pairing and association with an aversive outcome (unconditioned stimulus, US). However, fear responses are not often restricted to the initial CS+ − US association, but can be broadened to other stimuli and contexts that are similar or related to the CS, a process known as fear generalization. Furthermore, fear responses can be extinguished when the CS is repeatedly presented in the absence of the US, and thereby loses its predictive value. Through such extinction learning, a new, inhibitory CS+ − no US association is formed, that may suppress the original CS-US association. This extinction association is however often weaker than the CS-US association, and tests of extinction retention often show the recurrence of conditioned fear responses at a later moment (i.e. extinction recall). The neurobiology of these processes has been studied extensively in rodents and healthy humans, with studies showing that threat processing involves a network including the dorsal anterior cingulate, bilateral insula, and midbrain, while safety processing activates the ventromedial prefrontal cortex (vmPFC), hippocampi, and precuneus (Fullana et al., 2016; Milad & Quirk, 2012).

A recent meta-analysis found that anxiety disorder patients show dysregulated fear and extinction learning through enhanced fear responding (self-report and/or psychophysiological responses) to conditioned safety stimuli (CS-) that are not followed by a US, as well as smaller reductions in fear responses to the CS+ during extinction learning phases (Duits et al., 2015). Furthermore, a recent neuroimaging study has reported neurobiological alterations in fear acquisition and recall of the extinction memory, specifically demonstrating reduced activation in the vmPFC in individuals with anxiety disorders (Marin et al., 2017). However, no effort was made to differentiate between different types of anxiety disorders. Studies on fear generalization have also reported enhanced generalization in psychophysiology and/or neural activations in high trait anxious individuals, and patients suffering from PTSD or GAD (Kaczkurkin et al., 2016; Lissek et al., 2014; Greenberg et al., 2013; Haddad et al., 2012), while null findings have been reported (Torrents-Rodas et al., 2013; Tinoco-González et al., 2015). These dysregulations in safety learning, fear generalization, extinction learning and extinction recall may be reflective of general deficits in the inhibition of fear responses and inhibitory learning (Sijbrandij et al., 2013; Lissek, 2012; Graham & Milad, 2011).

Factor-analytic studies suggest that excessive fear and anxiety may form a spectrum of pathology, extending from diagnoses associated with more specific fears, such as specific phobia and discrete traumatization, to diagnoses associated with anxious-misery disorders such as GAD, major depressive disorder (MDD), and complex PTSD (Krueger, 1999; Clark & Watson, 2006; Watson, 2005). Such a spectrum can be observed in the startle potentiation response to threat, ranging from hyperresponsivity in phobic disorders to hypo-responsivity in anxious-misery disorders (Lang & McTeague, 2009; Lang et al., 2016; Lang et al., 2007; McTeague & Lang, 2012). Although OCD is separately classified, other disorders characterized by excessive fear or anxieties are grouped and studied together in the Diagnostic and Statistical Manual for Mental Disorders – 5th Edition (DSM-5) (Association AP, 2013) under the umbrella term 'anxiety disorders' and/or 'PTSD', and this may preclude finding specific pathological patterns across the fear-anxiety spectrum. Indeed, in fear learning, generalization, and extinction research, this fear-anxiety spectrum has received only limited attention.

Specifically, to date, it remains largely unknown if fear learning, fear generalization, extinction learning, and extinction recall are dysregulated in disorders on the fear-side of the fear-anxiety spectrum. Specific phobia (SP) is characterized by focal fear, and is therefore thought to represent a model fear disorder (Klahn et al., 2017). Remarkably, in specific phobia, fear learning has merely been investigated by three studies (Vriends et al., 2012; Schweckendiek et al., 2011), whereas threat-related generalization (Dymond et al., 2014) and extinction learning and recall (Mosig et al., 2014) were only examined by one study. Results of the fear learning studies suggest a different pattern of responses in SP compared to those reported in the meta-analytic study mentioned above (Duits et al., 2015). Specifically, the meta-analytic study showed indications of reduced CS+/CS- differentiation in subjective ratings and/or psychophysiology during fear conditioning in anxiety disorders and PTSD compared to healthy controls. In contrast, in SP, enhanced differential conditioning has been observed, as reflected by enhanced stimulus discrimination in valence ratings (Vriends et al., 2012; Mosig et al., 2014), higher psychophysiological hyper-responsitivity to phobia-relevant and phobia-irrelevant CS+ (Schweckendiek et al., 2011; Mosig et al., 2014), as well as increased fear circuitry activation to CS+ compared to CS- (Schweckendiek et al., 2011). However, enhanced differential conditioning was not reflected in all outcomes within each study. Furthermore, the one study on threat-related generalization reported higher threat-avoidance in response to phobia-relevant stimuli in spider phobic individuals compared to non-phobics (Dymond et al., 2014), while the study comparing SP and controls on extinction learning and recall study did not find any group differences (Mosig et al., 2014).

The current study builds on this previous work by systematically investigating whether excessive fear psychopathology (i.e. SP) is characterized by general alterations in behavioral and neural mechanisms of fear acquisition, acquisition retention, fear generalization, extinction learning, extinction retention. To minimize comorbidity and heterogeneity issues, we included individuals with spider phobia without comorbidities (SP; n = 46), thereby using the disorder as a model for fear-related symptoms to compare with healthy controls (HC; n = 48). All subjects underwent the same symptom measurements and a functional neuroimaging fear conditioning and generalization protocol, using abstract, phobia-irrelevant stimuli, in order to examine whether general deficits in fear-related processes could be observed beyond expected excessive fear responses to phobia-relevant stimuli. We hypothesized that individuals with SP would show increased self-reported fear and enhanced neural responding in threat-related regions to the CS + during fear acquisition, and reduced fear regulation-related activation in the vmPFC, reflecting enhanced fear generalization. It was also hypothesized that no alterations in extinction learning and extinction recall would be observed in those with SP relative to HCs.

2. Materials and methods

2.1. Participants

Data were acquired as part of a large randomized controlled trial investigating the effects of psychological therapy on psychopathology in emerging adulthood (Smartscan, Dutch Trial Register Number: NTR380). The current study included participants aged 16–25 years old with a specific phobia for spiders (SP), and healthy controls (HC). Participants were recruited via local advertisements. The SP group was required to meet the DSM-IV criteria for a specific phobia as confirmed by the MINI International Neuropsychiatric Interview (Lecrubier et al., 1997). Exclusion criteria for the SP group were any other current psychiatric diagnosis or current psychiatric treatment, and any past diagnosis other than an anxiety disorder. For HC, a current or past diagnosis or treatment were excluded. Exclusion criteria for both groups further existed of a history of neurological disease, use of psychotropic medication, left-handedness, and MRI contra-indications. The study was approved by the local medical ethics committee. All participants received full information about study procedures and provided informed consent before study onset. Parental consent was additionally obtained for minors (age < 18 years).

2.2. Psychopathology measures

Spider phobia severity was captured by two measures: