From fear extinction to exposure therapy: neural mechanisms and moderators of extinction

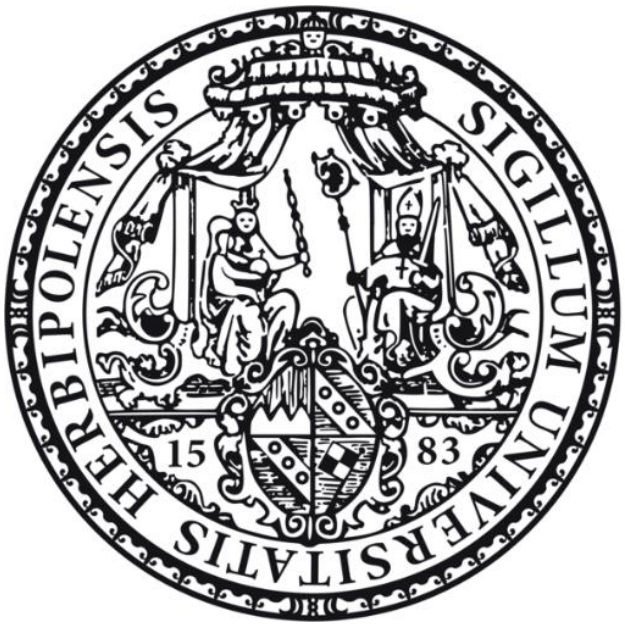
Von der Furchtextinktion zur Expositionstherapie: Neuronale Mechanismen und Moderatoren der Extinktion

Doctoral thesis for a doctoral degree at the

Graduate School of Life Sciences,

Julius-Maximilians-Universität Würzburg,

Section Neuroscience.



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"The illiterate of the 21st century will not be those who cannot read and write but those who cannot learn, unlearn, and relearn."

- Alvin Toffler-

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ABSTRACT

Emotional-associative learning processes such as fear conditioning and extinction are highly relevant to not only the development and maintenance of anxiety disorders (ADs), but also to their treatment. Extinction, as the laboratory analogue to behavioral exposure, is assumed a core process underlying the treatment of ADs. Although exposure-based treatments are highly effective for the average patient suffering from an AD, there remains a gap in treatment efficacy with over one third of patients failing to achieve clinically significant symptom relief. There is ergo a pressing need for intensified research regarding the underlying neural mechanisms of aberrant emotional-associative learning processes and the neurobiological moderators of treatment (non-)response in ADs.

The current thesis focuses on different applications of the fundamental principles of fear conditioning and extinction by using two example cases of ADs from two different multicenter trials. First, we targeted alterations in fear acquisition, extinction, and its recall as a function of psychopathology in panic disorder (PD) patients compared to healthy subjects using fMRI. Second, exposure-based therapy and pre-treatment patient characteristics exerting a moderating influence on this essential learning process later on (i.e. treatment outcome) were examined using multimodal functional and structural neuroimaging in spider phobia.

We observed aberrations in emotional-associative learning processes in PD patients compared to healthy subjects indicated by an accelerated fear acquisition and an attenuated extinction recall. Furthermore, pre-treatment differences related to defensive, regulatory, attentional, and perceptual processes may exert a moderating influence on treatment outcome to behavioral exposure in spider phobia. Although the current results need further replication, on an integrative meta level, results point to a hyperactive defensive network system and deficient emotion regulation processes (including extinction processes) and top-down control in ADs. This speaks in favor of transdiagnostic deficits in important functional domains in ADs.

Deficits in transdiagnostic domains such as emotion regulation processes could be targeted by enhancing extinction learning or by means of promising tools like neurofeedback. The detection of pre-treatment clinical response moderators, for instance via machine learning frameworks, may help in supporting clinical decision making on individually tailored treatment approaches or, respectively, to avoid ineffective treatment and its related financial costs. In the long run, the identification of neurobiological markers which are capable of detecting non-responders a priori represents an ultimate goal.

ZUSAMMENFASSUNG

Emotional-assoziative Lernprozesse wie Furchtkonditionierung und Extinktion sind für die Entstehung und Aufrechterhaltung, aber auch für die Behandlung von Angststörungen (AS) von hoher Relevanz. Extinktion, als Laboranalog der Verhaltensexposition, gilt als ein der Behandlung von AS zugrundeliegender Kernprozess. Obwohl expositionsbasierte Behandlungen für den durchschnittlichen Angstpatienten hoch wirksam sind, besteht weiterhin eine Behandlungslücke, da über ein Drittel der Patienten keine klinisch signifikante Verbesserung erzielt. Daher besteht ein dringender Bedarf an intensivierter Forschung hinsichtlich der neuronalen Grundlagen veränderter emotional-assoziativer Lernprozesse und der neurobiologischen Moderatoren des (Nicht-)Ansprechens bei der Behandlung von AS.

Die vorliegende Arbeit konzentriert sich daher auf verschiedene Anwendungen des grundlegenden Prinzips der Furchtkonditionierung und Extinktion anhand zweier Anwendungsbeispiele aus zwei multizentrischen Studien. Zuerst wurden psychopathologisch bedingte Veränderungen der basalen Mechanismen des Furchtlernens, der Extinktion und des Extinktionsabrufs bei Patienten mit Panikstörung im Vergleich zu gesunden Probanden untersucht. Anschließend wurde mittels multimodaler funktioneller und struktureller Bildgebung der moderierende Einfluss von Patientencharakteristika vor der Behandlung auf das spätere Behandlungsergebnis bei Spinnenphobie untersucht.

Bei Panikpatienten wurden Abweichungen in emotional-assoziativen Lernprozessen im Sinne einer beschleunigten Furchtakquisition und eines abgeschwächten Extinktionsabrufs beobachtet. Bei Spinnenphobikern üben Unterschiede in Bezug auf Defensiv-, Regulations-, Aufmerksamkeits- und Wahrnehmungsprozesse vor der Behandlung möglicherweise einen moderierenden Einfluss auf das Behandlungsergebnis einer Verhaltensexposition aus. Obwohl diese Ergebnisse noch weiterer Replikation bedürfen, weisen sie auf der transdiagnostischen Metaebene auf ein hyperaktives Defensivnetzwerk und mangelhafte Emotionsregulationsprozesse (einschließlich Extinktionsprozesse) sowie Top-Down-Kontrolle bei Angstpatienten hin.

Defizite in transdiagnostischen Bereichen wie Emotionsregulationsprozessen könnten durch eine Verbesserung des Extinktionslernens oder durch vielversprechende Verfahren wie Neurofeedback angegangen werden. Die Identifizierung von Moderatoren und neurobiologischen Markern des Behandlungs(miss-)erfolgs bereits vor der Behandlung, z.B. durch maschinelles Lernen, könnte personalisierte Behandlungsansätze unterstützen bzw. ineffektive Behandlungen und damit verbundene Kosten ersparen und stellt somit ein Langzeitziel dar.

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  Schwarzmeier, H., Kleint, N. I., Wittchen, H.-U., Ströhle, A., Hamm, A. O., & Lueken, U. (2019). Characterizing the nature of emotional-associative learning deficits in panic disorder: An fMRI study on fear conditioning, extinction training and recall. *European Neuropsychopharmacology, 29*(2), 306-318.

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  Schwarzmeier, H., Leehr, E. J., Böhnlein, J., Seeger, F. R., Roesmann, K., Gathmann, B., Herrmann, M. J., Siminski, N., Junghöfer, M., Straube, T., Grotegerd, D., & Dannlowski, U. (2020). Theranostic markers for personalized therapy of spider phobia: Methods of a bicentric external cross-validation machine learning approach. *International Journal of Methods in Psychiatric Research, 29* (2), e1791.

I. THEORETICAL BACKGROUND

1. Introduction

"Mental disorders are the core health challenge of the 21st century."

(Wittchen et al., 2011, p. 670)

This statement actually sums up a multitude of challenges – considering that there are plenty of groups of disorders encompassing even more specific diagnoses requiring preventive, therapeutic, and rehabilitative approaches adaptable to different intensities, subgroups, and age groups. The non-existence of absolute cure, the lack of preventive interventions, and the fact that existing effective treatments are nonetheless not in all cases suitable, emphasizes the immediate need for more innovative research on all levels (Wittchen et al., 2011).

There are central questions arising in the field of studying mental disorders, or more specifically, anxiety disorders (ADs). What distinguishes individuals who develop an AD from those who do not under comparable circumstances? And which factors are decisive, if a person will benefit sufficiently from treatment or not?

Parallels regarding the neurobiology, phenomenology, psychotherapeutic, and pharmacological treatments of ADs hint at the contribution of common neurobiological mechanisms in their origination. With mounting insight of the neurobiological underpinnings of mental processes and disorders, we are aiming at theory integration across psychiatric disorders (Javanbakht, 2019).

Current research is beginning to follow a more dimensional approach instead of a strictly categorical and symptom-based approach, emphasizing the shared underlying mechanisms across mental disorders. Contemporary diagnostic systems for mental disorders were introduced before neuroscientific tools were available. Despite having enhanced the reliability of psychiatric classification, progress towards the detection of disease etiologies and novel treatment and prevention approaches could profit from alternative conceptualizations of mental disorders. The Research Domain Criteria (RDoC) initiative is the centerpiece of the National Institute of Mental Health´s (NIMH) effort to achieve the goal of developing new methods to classify mental disorders for research purposes. Examining the genetic, neural, and behavioral features of mental disorders, the integrative RDoC approach includes various domains like cognition, negative and positive valence systems, or social processes. Focusing on neural circuitry induced by the accumulating evidence of the neurodevelopmental nature of many

disorders, the RDoC approach promises well to promote our understanding of the nature of mental disorders (Morris & Cuthbert, 2012).

Thus, the current thesis focuses on the shared underlying mechanisms in both etiology and treatment of ADs – namely fear conditioning and extinction processes. This basic form of associative learning represents a translational model for studying pathological anxiety and its treatment. Examining individual differences in fear conditioning and extinction may therefore not only inform us about the development and maintenance of ADs, but also about the predictive value of the very same for treatment outcome.

This first chapter contains a short overview of the epidemiology, clinics, and neural substrates of ADs in general and more specific, panic disorder (PD) and specific phobia (SP) are shortly outlined, since these disorders are substantial part of the included experiments in this thesis. Furthermore, etiological models, especially fear conditioning as a translational model, are elucidated. Subsequently, treatment of ADs and moderators of treatment outcome are presented.

The introductory part is followed by two empirical studies. First, the nature of basic emotional-associative learning processes in PD is examined in comparison to healthy individuals. Second, neural correlates of fear processing and moderators of treatment response towards behavioral exposure in spider phobia are investigated.

The last part provides an overarching discussion and integration of the results and gives an outlook on future research directions.

2. Epidemiology, clinics, and neural mechanisms of anxiety disorders

2.1. Fear, anxiety, and anxiety disorders

The term ADs subsumes different disorders that share central features of excessive fear and anxiety. Although showing substantial overlap concerning subjective, behavioral, physiological, and neurological aspects, these two constructs also differ in respect to certain characteristics. Fear is the phasic emotional reaction to a real or a perceived imminent threat and associated with high autonomic arousal for fight or flight, and an urge to escape in response to thoughts of immediate threat. Anxiety is the more prolonged anticipation of future threat and therefore characterized by muscle tension, heightened vigilance, and avoidant, cautious behavior in preparation for future danger (American Psychiatric Association, 2013).

When the anxiety or fear response is excessive or occurs without real threat or danger, either immediate or in the future, ADs can develop. Fear and anxiety are both part of all ADs, however, there are suggestions that some ADs like PD and SP are more fear-based disorders,

while posttraumatic stress disorder (PTSD) and generalized anxiety disorder (GAD) are more anxiety-based disorders (Duval, Javanbakht, & Liberzon, 2015).

2.2. Epidemiology and burden of anxiety disorders

ADs constitute the most prevalent group of mental disorders with a 12-month prevalence of 14%, equaling 61.5 million people in Europe, with females being affected about two to three-times more frequently than males (Wittchen et al., 2011). A meta-analytic review analyzing data from 23 separate studies (N = 2892) yielded a large effect size indicating poorer quality of life (QOL) among AD patients compared to controls. This effect was observed transdiagnostically for all ADs and the QOL domains of mental health and social functioning were linked to the highest impairment levels among AD patients (Olatunji, Cisler, & Tolin, 2007).

In developed countries, mental disorders are liable for more than 15% of the disease burden, exceeding all forms of cancer. Despite that, the proportion of research funds invested in mental health is only 7% in North America and 2% in the European Union according to estimates (Holmes, Craske, & Graybiel, 2014). Mental disorders are the quantitatively most disabling group and since the disability burden – and alongside the societal burden – will further increase as a consequence of increased life expectancy, we are in urgent need of solutions (Wittchen et al., 2011).

Mental disorders are furthermore extremely costly. Especially indirect costs arising from sick days or early retirement prevail direct costs of health care (Wittchen et al., 2011). Total European annual cost of brain disorders (mental and neurologic disorders) was €798 billion in 2010: 37% covered by direct health care cost, 23% by direct non-medical cost, and 40% by indirect cost. Total annual cost for ADs alone was €74.4 billion. Brain disorders cause presumably one third of all health-related costs, and are assumed to be the number one economic burden and challenge for European health care systems, today and in the future. This is even more acute, since the burden of brain disorders is expected to further increase. These figures clearly show the pressing need and importance of basic research concerning the causes of brain disorders and their treatment, and of course with a focus on prevention, bound to improved etiological knowledge (Gustavsson et al., 2011; Olesen, Gustavsson, Svensson, Wittchen, & Jönsson, 2012).

2.3. Neural substrates of anxiety disorders

Cross-diagnostic meta-analyses suggest an abnormally elevated fear response as a key feature of ADs. This key feature results in shared symptomatology among ADs (Etkin & Wager, 2007).

Major areas of anatomical and functional significance that have been identified transdiagnostically by multiple studies, constitute the amygdala, the insula, the anterior cingulate cortex (ACC), and the hippocampus, as well as the medial prefrontal cortex (mPFC) and the dorsolateral PFC (dlPFC) (e.g. Damsa, Kosel, & Moussally, 2009; Duval et al., 2015; Etkin & Wager, 2007). These regions are also involved in attention modulation and emotion regulation, and evidence hints at a deficit in fear regulation circuitry in anxiety (Duval et al., 2015).

To maintain emotional health, however, the individual needs effective systems to regulate fear expression by determining under which conditions fear expression is appropriate and of advantage. Emotion regulation is therefore closely intertwined with the concept of inhibition. Inhibition is carried out by higher cortical areas, which exert inhibitory control over subcortical areas responsible for generating prepotent emotional responses. Fear extinction for example represents a clinically relevant example of emotion regulation via inhibitory learning processes. In ADs, individuals seem to be unable to inhibit their expression of fear associations in the absence of danger, likely reflecting pathological emotion regulation systems (Quirk, 2007).

Emotion regulation in healthy individuals can be described via a limbic-mPFC feedback loop. A negative emotional stimulus is first recorded in two core limbic structures, the amygdala and the insula, which can then direct and modulate activity in various target regions like the sensory cortex, the periaqueductal grey (PAG), the hypothalamus, and the hippocampus. Further inspection and evaluation of the negative stimuli takes place in the dorsal ACC (dACC) and the dorsomedial PFC (dmPFC), regions that are directly informed by core limbic structures and indirectly via ventral frontal regions innervated from core limbic structures. This results in a detailed emotional appraisal of the stimulus, which cannot be carried out by the amygdala or the insula. This appraisal can also be accompanied by conscious awareness. Stimulus information is then sent to regulatory regions in the ventral ACC and the ventromedial PFC (vmPFC), either via direct connections from limbic structures or via projections from the dACC and dmPFC. These regulatory regions now send feedback to limbic structures again, leading to an appropriate regulatory response, i.e. either inhibiting or enhancing limbic activation and processing (Etkin, 2010).

Concerning ADs, evidence suggests transdiagnostic deviations within elements of this limbic-mPFC feedback loop. Individuals with ADs (except for obsessive-compulsive disorder; OCD) have consistently been found to show hyperactivation of the amygdala and insula compared to healthy individuals. This hyperactivation can be related to symptoms like

hyperarousal and hypervigilance, both often seen in ADs. In addition, there has also been noted a hypoactivation in dorsal and ventral regions of the mPFC related to regulatory mechanisms, hence reflecting an impaired regulation or dysregulation of negative affect (Etkin, 2010). Thus, there seems to be an imbalance in this dual-process model of emotion regulation, with an aberrantly high bottom-up limbic activation (emotion generation) and an impaired, insufficient top-down control by prefrontal regions (emotion regulation) in individuals with ADs (Marwood, Wise, Perkins, & Cleare, 2018; Quirk, 2007). Connectivity analyses across ADs are in line with that, demonstrating decreased connectivity between emotion-generating areas (amygdala, insula) and regulatory cortical areas (mPFC, rostral ACC) (Duval et al., 2015).

To sum it up, common patterns of hyperactivation in emotion-generating regions (e.g. amygdala, insula) and hypoactivation in prefrontal/regulatory regions across various ADs are found in the literature. Intriguingly, there is also mounting evidence of distinct disorder-specific signatures, e.g. increased recruitment of emotion-generating regions in PD and SP, and higher involvement of prefrontal regions in GAD and PTSD (Duval et al., 2015).

However, due to the low statistical power of individual studies, the variations in task design, patient and diagnostic characteristics, imaging modality, and last but not least in analytic approaches, results across studies on the neurobiology and neurocircuitry of ADs have often been inconsistent (Etkin & Wager, 2007). There are still many gaps regarding current knowledge on common and distinct transdiagnostic neurofunctional patterns in ADs, especially concerning differences in emotion-generating and emotion-regulating brain regions and their interconnections (Duval et al., 2015).

2.4. Panic disorder

Hallmark symptoms of PD are unexpected (“out of the blue”) recurrent panic attacks and associated persistent worries about experiencing a panic attack again. Panic attacks are characterized by a sudden onset (peak within approx. 10 minutes) of acute apprehension, fearfulness, or terror, often accompanied with feelings of impending doom despite the absence of real danger. During these discrete periods, at least four symptoms like shortness of breath, sweating, trembling, chest pain, palpitations, choking sensations, nausea or abdominal distress, dizziness, derealization or depersonalization, fear of losing control or going crazy, and a fear of dying, co-occur. PD is classified in PD without or with agoraphobia (PD/AG). Agoraphobia is characterized by symptoms of anxiety or avoidance of situations or places where it might be difficult or embarrassing to escape from, or where help may not be available in the case of a panic attack. Comorbidity with other ADs like SP or GAD, major depressive disorder (MDD) or substance-related disorders is common (American Psychiatric Association, 2000, 2013).

PD shows a 12-month prevalence of 1.8%, agoraphobia approximately 2% in Europe (Wittchen et al., 2011) and between 0.5 - 1.5% in the USA, with a lifetime prevalence between 1 - 3.5% (American Psychiatric Association, 2000). 12-month prevalence for panic attacks ranges between 2.7% - 3.3% in European countries and 11.2% in the USA. Median age of onset for PD in the USA is 20-24 years. PD is diagnosed twice as often and PD/AG three times as often in women as in men and shows a strong familial pattern. PD usually has a chronic course and often leads to high levels of physical, social, and occupational disability and associated economic costs (American Psychiatric Association, 2013).

2.5. Specific phobia

The hallmark of SP is clinically significant anxiety in response to exposure to a specific feared object or situation, often resulting in avoidance behavior. SP can also involve concerns about loss of control, panicking, somatic manifestation of anxiety, and fainting when exposed to the feared object or situation. If escape seems impossible and the individual is ergo forced to remain in the situation, full-blown panic attacks can occur (American Psychiatric Association, 2000). There are different subtypes: the animal type, natural environment type (e.g. heights, water), blood-injection-injury type (B-I-I), situational type (e.g. airplanes, elevators), and other type subsuming those not belonging to the types mentioned before (e.g. fear of choking, contracting illness etc.).

SPs are the most frequent ADs in Europe with a 12-month prevalence of 6.4% (Wittchen et al., 2011) and show the highest lifetime-prevalence among ADs in the USA (Kessler et al., 2005), although prevalence rates decline with advancing age. SPs typically show a childhood onset. In general, the sex ratio is 2:1 for women compared to men, but it differs depending on the phobic subtype. In the animal, natural environment, and situational type, about 75% - 90% are female and approx. 55% - 77% in the B-I-I type. Having one phobia of a specific subtype increases the likelihood of having another phobia of the same subtype, and SP often co-occurs with other ADs, mood disorders, and substance-related disorders. Overall, there is an increased risk for family members of affected individuals to have a SP themselves. Despite the fact that phobias are common, they rarely cause sufficient impairment or distress to fulfill a diagnosis of SP (American Psychiatric Association, 2000). However, SP leads to similar patterns of impairment in psychosocial, occupational and interpersonal functioning and decreased QOL as in other ADs (American Psychiatric Association, 2013).

3. Defensive systems and fear learning

3.1. Fear processing and defensive networks in the brain

Fear is closely associated with the survival of species as it reflects a brain state which elicits and orchestrates defense reactions to possible threat. The organism (from insects to humans) must be equipped with neural circuits able to learn, detect, and rapidly respond to threat in an appropriate way in order to avoid harm. Defense circuits are evolutionary preserved and act by facilitating certain kinds of responses while inhibiting others (Bentz & Schiller, 2015; Marek & Sah, 2018; Tovote, Fadok, & Lüthi, 2015).

These hardwired response tendencies have been retained by natural selection as they promote survival and reproductive success. Thus, the neuronal basis of fear is conserved across species and corroborated by numerous findings of animal and human studies (Phelps & LeDoux, 2005). Threat-related stimuli can be either innate or learned and there is evidence that the organism might be innately prepared to certain stimuli like snakes or spiders which can be associated with threat more easily (Bentz & Schiller, 2015; Öhman & Mineka, 2001). In contrast, emotional-associative learning (e.g. fear conditioning and extinction) is a basic mechanism how an organism can flexibly adapt to changing environmental dangers and thus represents an ontogenetic route of defensive reactivity. Exposure-based treatments take advantage of these basic learning mechanisms in order to alleviate fear and anxiety.

Physiological fear responses leading to activity changes of the limbic system activate the sympathetic nervous system which triggers a fight-or-flight response. This response again causes an increase in heart rate, blood pressure, and skin conductance accompanied by pupil dilation and changes in posture and mobility. This time-limited physiological and behavioral state returns to baseline after some time (Marek & Sah, 2018).

The neural systems coordinating distinct defensive threat responses include areas like the mPFC, amygdaloid and hypothalamic nuclei, hippocampal formation, and the midbrain central grey (Canteras, Resstel, Bertoglio, de Pádua Carobrez, & Guimarães, 2010). Of note, fear responses do not result from the neural activity of single brain structures alone but rather from the orchestrated activity of multiple nuclei, mediated by synaptic connections between them to elicit a fear response (Marek & Sah, 2018).

A prominent model to describe how the brain orchestrates defensive reactions follows the concept of a low (subcortical) and high (cortical) road, describing different sensory pathways (LeDoux, 1994). On the low road, visual input is first sent to the midbrain superior colliculus the before being relayed to the amygdala via the pulvinar nucleus. This is assumed a

subconscious, imprecise and fast pathway which localizes objects and elicits automatic reactions. On the high road, visual input from the retina is relayed to the visual cortex via the lateral geniculate nucleus, a brain region in the thalamus. Visual input is processed through several areas of the visual cortex (V1, V2, V4) and the temporal cortex before it reaches the amygdala, whereupon autonomic and endocrine mediators in lower midbrain and brainstem structures are engaged. This is considered an evolutionarily later consciously aware and precise, but also slower, visual system which identifies objects (Carr, 2015; LeDoux, 1994; Pessoa & Adolphs, 2010). The amygdala is connected to all areas of the ventral visual stream via feedback projections. These amygdalocortical projections can exert modulatory control over visual processing at all levels of the ventral stream cortical hierarchy. This may be especially important in highly emotional situations, e.g. by directing visual attention towards environmental salient and potentially harmful stimuli (Amaral, Behniea, & Kelly, 2003).

Fear is then triggered when a danger or a stimulus predicting immediate danger (innately or conditioned) is perceived. Fear ergo serves the purpose to prepare the organism to face this threat. However, dysfunctional fear processing can lead to mental disorders when the dimension of fear outweighs the danger or possibility of harm (Garcia, 2017).

To sum it up, although fear contributes to survival, difficulties in regulating threat responses can interfere with goal-directed activities and represent the hallmark of ADs (Meyer et al., 2019). Therefore, the neural underpinnings of defensive behavior are relevant to both basic research and its clinical translation (Patrick et al., 2019).

3.2. Fear conditioning as a translational model of fear learning

The concept of fear conditioning is a highly adaptive cross-species phenomenon that helps to detect warning signals for impending threat (Beckers, Krypotos, Boddez, Effting, & Kindt, 2013). Fear-associated learning (fear conditioning and extinction) has been widely used to elucidate the neurocircuitry underlying emotional learning. Since studies in animals preceded those in humans by years, research in the last years was facilitated by a rodent-to-human translational approach (Greco & Liberzon, 2016; Milad & Quirk, 2012). Thanks to animal studies identifying the structures and systems involved in emotional processing, the basis for our understanding of the corresponding neurocircuitry in humans could be established (Greco & Liberzon, 2016).

Fear conditioning describes an associative learning process whereby a naturally benign stimulus acquires anxiogenic properties by virtue of its pairing with a naturally aversive stimulus which evokes an unconditioned response (UCR, e.g. fear) (Lissek & van Meurs, 2015). In the most basic form, a neutral conditioned stimulus (CS, e.g. tone) is repetitively presented

together with an aversive unconditioned stimulus (US, e.g. electrical shock). After several presentations, the CS alone is capable of eliciting a conditioned response (CR) in absence of the US (Greco & Liberzon, 2016).

Repeated presentation of the CS without the aversive US will lead to a gradual decline of the CR as the individual learns that the CS has no predictive value for the US anymore. This active learning process of extinction training does not result in an erasure of the conditioned fear memory itself (CS-US association, excitatory link), but it creates a new memory trace, the extinction memory (CS-no-US association, inhibitory link), which is now capable of inhibiting the CR (Giustino & Maren, 2015; Milad & Quirk, 2012; Myers & Davis, 2007; Phelps, Delgado, Nearing, & LeDoux, 2004). Inhibitory learning is ergo essential to extinction (Craske et al., 2008). Extinction retention describes the consolidation of the extinction learning into long-term memory (Berry, Rosenfield, & Smits, 2009). Extinction training and the retention of extinction are therefore two dissociable processes. In animal studies, extinction retention is typically tested 24h after the completion of extinction training using delayed fear extinction tasks (Lueken & Maslowski, 2012). In humans, though, only few studies have examined the dissociation between performance (i.e. extinction training) and actual learning (i.e. extinction retention and recall) so far (Brown, LeBeau, Chat, & Craske, 2017).

When the CS is then encountered again after extinction training, both memory traces can be activated. The magnitude of the fear reactions depends on the extent to which the extinction memory is activated (Milad, Rauch, Pitman, & Quirk, 2006). Hence, extinction recall describes the retrieval and expression of the extinction memory after a time delay (Milad et al., 2009). The assumption that extinction does not lead to an erasure of the conditioning memory is based on three key phenomena. First, the CR to the CS can reappear with a passage of time (spontaneous recovery). Second, when the CS is presented in a different context from the one in which extinction training originally took place, the CR can return (renewal). Third, the CR can be restored by unexpectedly delivering the US following extinction (reinstatement). Renewal and reinstatement demonstrate that the CS retains its capability to elicit the CR following extinction (Marek & Sah, 2018). Ergo, the return of fear (ROF) is the reappearance of fear that has been partially or completely extinguished (Rachman, 1989).

The neural substrates of fear acquisition are well described in both rodents and humans (Maren & Quirk, 2004), a schematic overview is illustrated in figure 1. The basolateral complex of the amygdala (BLA) represents the main structure where information about the CS and US converge (LeDoux, 2000), as it receives sensory and contextual inputs from somatosensory cortex, thalamus, and hippocampus (Greco & Liberzon, 2016). The prelimbic (PL) subdivision

of the mPFC is thought to regulate the expression of learned fear in rodents (Giustino & Maren, 2015; Maren et al., 2013; Quirk & Mueller, 2008) and the dACC as its homologue in humans (Giustino & Maren, 2015; Milad, Quirk, et al., 2007). The central amygdala (CEA) represents another core structure involved in fear acquisition and expression (Duvarci & Pare, 2014) and receives, among other direct inputs, information from the BLA (Greco & Liberzon, 2016). While fear acquisition requires the lateral subdivision of the CEA, conditioned fear responses are driven by output neurons in the medial subdivision projecting to the brainstem and the hypothalamus, where then conditioned autonomic and motor responses are orchestrated (Ciocchi et al., 2010). Lesions of the amygdala were shown to block the acquisition as well as the expression of CRs in rodents (Hitchcock & Davis, 1986; Phillips & LeDoux, 1992) and also in humans (Bechara et al., 1995; LaBar, LeDoux, Spencer, & Phelps, 1995).

However, in recent meta-analyses of fear conditioning studies in humans, the amygdala was not consistently found to be activated during fear acquisition (Fullana et al., 2016; Sehlmeyer et al., 2009). This sometimes inconsistent translation to human neuroimaging does not question the role of the regions itself, but is rather due to several methodological factors (Fullana et al., 2020). Other additional regions found to be consistently activated during fear acquisition are, among others, the ACC, (anterior) insula, frontal operculum, supplementary motor area (SMA), somatosensory cortex, premotor cortex, cerebellum, ventral striatum, and the dlPFC (Fullana et al., 2016).

Fear extinction engages the amygdala, the infralimbic (IL) division of the mPFC, and the hippocampus (Milad & Quirk, 2012). Evidence suggests significant changes in amygdala microcircuitry during extinction and that the IL cortex is involved in some of these changes (Delamater & Westbrook, 2014). The IL cortex and its human homologue, the vmPFC, are thought to regulate fear suppression (Giustino & Maren, 2015), i.e. retention and/or expression of fear extinction (Myers & Davis, 2007). Evidence suggests that the presentation of an extinguished stimulus activates the hippocampus, which in turn activates the IL cortex. The IL cortex activates inhibitory interneurons in the BLA and/or the inhibitory intercalated cell masses (ITC) surrounding the BLA, which now inhibit the CEA, and thus, conditioned fear responding (Herry et al., 2010).

PL/dACC and IL/vmPFC are thus able to gate the expression of amygdala-dependent fear memories via divergent projections. While the PL/dACC connects to excitatory areas and stimulates fear expression, the IL/vmPFC cortex connects to inhibitory centers within the amygdala (Milad & Quirk, 2012). Other additional regions found to be consistently activated

during fear extinction are, among others, the ACC, posterior cingulate cortex (PCC), mPFC, insular cortex extending into frontal operculum, dlPFC, and thalamus (Fullana et al., 2018).

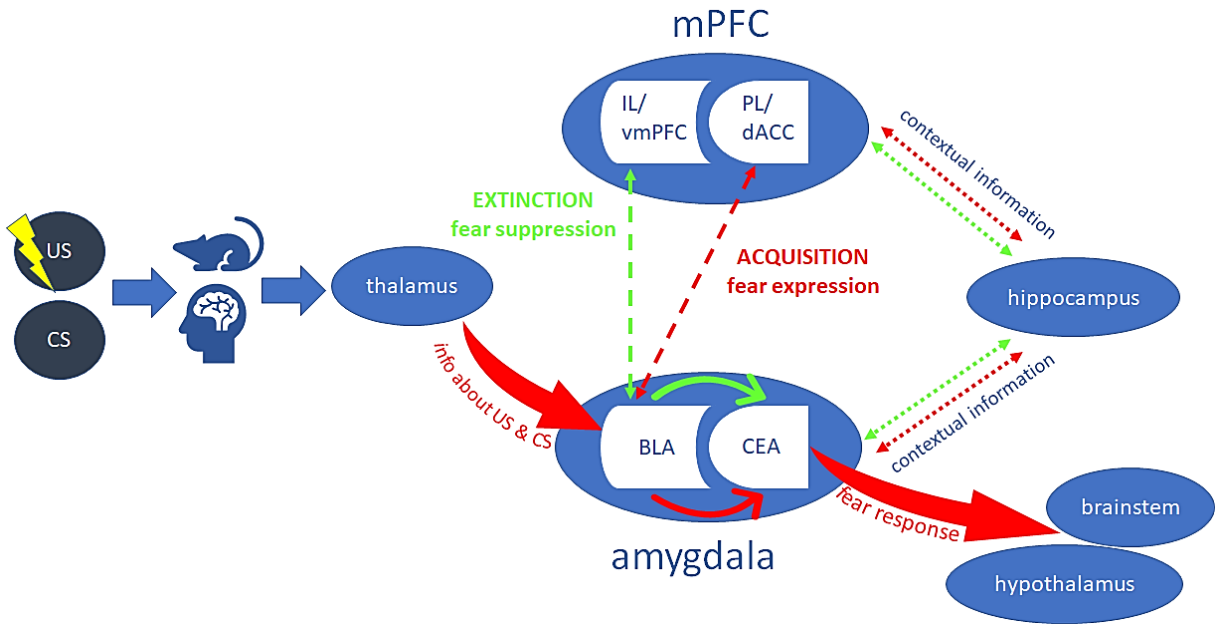

Figure 1. Schematic overview of the fear conditioning and extinction circuitry. Information about the US and the CS converge in the BLA. The PL projects to the BLA, which in turn excites the CEA, leading to fear expression. The IL projects to inhibitory interneurons in the BLA and/or the inhibitory intercalated cell masses surrounding the BLA, which inhibit the CEA and ergo result in fear suppression. The hippocampus integrates relevant contextual information. US: unconditioned stimulus; CS: conditioned stimulus; BLA: basolateral amygdala; CEA: central amygdala; IL: infralimbic cortex; vmPFC: ventromedial prefrontal cortex; PL: prelimbic cortex; dACC: dorsal anterior cingulate cortex; mPFC: medial prefrontal cortex.

The hippocampus is considered a key mediator of learned fear, integrating contextual information during conditioning (Giustino & Maren, 2015), consolidating extinction (Quirk & Mueller, 2008), and guiding retrieval of fear extinction memory, i.e. extinction recall, by the use of contexts (Maren & Holmes, 2016). It has strong connections with the IL/vmPFC and the amygdala (Delamater & Westbrook, 2014). Accordingly, lesions of the hippocampus have been shown to attenuate fear responding to a previously aversively conditioned context (Phillips & LeDoux, 1992). Due to its context-sensitivity, the hippocampus may thus have an either excitatory or inhibitory effect on fear responding, depending on the encoded context (Milad & Quirk, 2012). If an extinguished cue is presented in a context different from the extinction context, the hippocampus may not be activated, leading to a return of conditioned responding, i.e. the ROF (Quirk & Mueller, 2008). In turn, inactivation of the hippocampus impairs fear renewal (Maren et al., 2013).

Together with the hippocampus, the IL cortex/vmPFC represents another essential region in the recall of extinction in both rodents and humans (Greco & Liberzon, 2016; Kalisch et al., 2006; Phelps et al., 2004; Quirk & Mueller, 2008). Lesions of the IL cortex/vmPFC in

rats did not impair acquiring fear extinction, however, the next day these rats were not able to retrieve their extinction memory. Thus, the vmPFC is not necessary for the expression of extinction, but it is essential for recalling extinction learning after a delay (Quirk, Russo, Barron, & Lebron, 2000). In humans, thickness of the vmPFC was positively correlated with extinction recall (Milad et al., 2005) and a stronger activation of the vmPFC was associated with a better inhibition of the CR during extinction recall (Milad, Wright, et al., 2007). Additionally, lesions of the vmPFC in humans led to potentiated amygdala responses to aversive stimuli in comparison to healthy subjects, thus providing further evidence for the pivotal role of the mPFC in regulating amygdalar actitvity (Motzkin, Philippi, Wolf, Baskaya, & Koenigs, 2015).

Taken together, the amygdala, hippocampus, and mPFC are highly bidirectional connected brain regions occupying key positions in fear processing (Marek & Sah, 2018; Tovote et al., 2015). Stimulation and lesion studies unraveled the contribution of these regions to fear learning and extinction in animal (Marek, Strobel, Bredy, & Sah, 2013) and in human studies, suggesting shared underlying neural circuitry conserved across species. Nevertheless, there are still clearly many gaps left in our understanding (Marek & Sah, 2018).

3.3. Fear conditioning across anxiety disorders

The study of ADs in humans has benefited enormously from functional neuroimaging approaches. Altered fear learning seems to play a crucial role in the development of ADs. Of note, brain regions that take part in associative fear learning (primarily amygdala, ACC, and hippocampus) overlap to a large extent with those involved in the pathophysiology of ADs (Greco & Liberzon, 2016). Evidence suggests that aberrations in this circuit are a cross-diagnostic feature of ADs, forming the basis of their shared psychopathology and high degree of comorbidity with other ADs (Milad, Rosenbaum, & Simon, 2014).

Fear conditioning and extinction, i.e. associative learning processes, are thought to represent an etiological model for ADs (Lissek et al., 2005; Mineka & Oehlberg, 2008). Altered emotional-associative learning, like enhanced fear acquisition and/or attenuated extinction learning and/or recall, can result in exaggerated and inadequate fears, as seen in the ADs (Lueken & Maslowski, 2012). For instance, a recent study suggests that spider phobia may be characterized by stronger differential fear retention and altered brain activation patterns during fear acquisition and extinction recall (Lange et al., 2020).

A potential etiological factor concerning the development of ADs is the individual fear conditionability, which describes the general ability of a person to learn (and extinguish) the association of a neutral CS with an aversive US. Fear conditionability has been shown to be

elevated in individuals with high trait anxiety or patients with ADs (Vriends et al., 2011). This hyper-conditionability constitutes a disposition towards acquiring abnormally strong associations and a resulting enhanced resistance to extinction. Failure to extinguish describes the persistence of fear to stimuli no longer indicative of environmental danger, and therefore, constitutes a maladaptive expression of anxiety (Lissek & van Meurs, 2015). Anxiety patients also tend to show increased fear responses to the CS- during acquisition compared to healthy controls (HC). This might reflect an overgeneralization, which may contribute to generalize learned fear responses more easily to other similar, but neutral stimuli (Duits et al., 2015). In addition, individuals with ADs typically exhibit diminished affective discrimination between conditioned threat and safety cues. Affective discrimination describes the ability to selectively demonstrate fear to dangerous but not safe situations (Cooper, Grillon, & Lissek, 2018).

Several studies found heightened fear reactions to the CS+ (i.e. the threat cue) during fear extinction in AD patients compared to HC (Duits et al., 2015; Lissek et al., 2005) and ergo support the idea of deficient extinction as a central mechanism for both developing and also treating ADs (Craske et al., 2008). This deficit in extinguishing conditioned fear may conduce to the intensity, generalization, and persistence of pathological anxiety (Heinig et al., 2017) and highlights the clinical relevance of extinction. The inability to extinguish or inhibit maladaptive defense responses is a transdiagnostic feature of all ADs, i.e. a dysregulation of inhibitory learning (Bentz & Schiller, 2015; Craske, Hermans, & Vervliet, 2018). Accordingly, findings point to an involvement of insufficient top–down regulation processes of conditioned defense reactions together with difficulties in identifying safe contexts (Bentz & Schiller, 2015).

However, supporting evidence has been found for all these theories from heightened conditionablity, to impaired extinction or resp. safety learning, to a overgeneralization of fear learning, and to a failure of associating stimuli with the US leading to chronic threat perception in ADs. This poses the even more intriguing question if there´s an underlying mechanism, unifying all of these observed phenomena (Vervliet, Craske, & Hermans, 2013).

4. Fear extinction and exposure treatment

4.1. Extinction as key mechanism of exposure-based treatment

Apart from their assumed role in the development of ADs, fear-learning variables can also make their contribution to the treatment of ADs (Forcadell et al., 2017). Extinction is the laboratory analogue of behavioral exposure (Bouton, Mineka, & Barlow, 2001; Craske et al., 2008) and is suggested to be one of the core processes underlying the treatment of ADs (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014). It operates via error correction mechanisms which

update the associative strength of a CS when the US does not occur; the greater the discrepancy between the predicted and the actually occurring, the larger the amount of associative change (Treanor & Barry, 2017).

Exaggerated and inappropriate threat responses as a hallmark of ADs often result in avoidance behaviors and functional impairment (Britton, Evans, & Hernandez, 2014). Avoidance behaviors are assumed to be responsible for preventing the extinction of fear and therefore, play an important part in the maintenance and recurrence of ADs. Following this, exposure-based treatment for ADs aims to target these maladaptive avoidance behaviors and by doing so, allowing extinction learning to take place (de Jong, Lommen, de Jong, & Nauta, 2019). Extinction learning is a central mechanism for achieving a fear reduction by means of exposure (Pittig, van den Berg, & Vervliet, 2016).

A unique characteristic of extinction/exposure research represents the translation from animal laboratory studies, to laboratory studies of healthy humans, to subclinical high-anxious humans, and to laboratory and treatment studies in clinical samples (Craske et al., 2018). Using fear extinction as a model can be seen twofold beneficial: by providing a direct measure of an underlying core dysfunction in ADs and by paralleling the underlying mechanism of exposure therapy and fear inhibition (Milad et al., 2014). Another advantage is the cross-species validity, showing comparable overlap of the neural underpinnings in humans and rodents (Delgado, Nearing, LeDoux, & Phelps, 2008), thereby shedding additional light on basic learning mechanisms through studies not initially feasible in humans (Milad et al., 2014). This allows for “bench-to-bedside” translation of basic research to therapeutic interventions (Myers & Davis, 2007).

To better understand the active components of exposure therapy, it is necessary to learn more about the neurobiological basis of emotional-associative learning in general – and even more important – about the aberrations in patients suffering from ADs. Following a translational perspective, knowledge about neural mechanisms of fear extinction learning and recall may contribute to improving exposure-based therapies (Lueken & Maslowski, 2012). Therefore, the study of the mechanisms of fear inhibition, and also the identification of interventions to facilitate inhibitory learning can inform clinical interventions for ADs (Myers & Davis, 2007). Current research focuses on strategies to enhance fear extinction learning and thereby, optimize exposure-based treatments for ADs (Pittig et al., 2016).

Furthermore, individual differences in fear extinction and recall may have a predictive value regarding treatment outcome and relapse. Targeting these processes could help in improving the efficacy of exposure-based procedures (Craske et al., 2014). Although the

translation from fear conditioning and extinction for exposure therapy is very well supported by research, extinction/exposure research has its challenges. One major question that remains is, why not all patients benefit sufficiently from exposure treatment, or experience a ROF, or even full relapse. Targeting alterations in the neural circuitry subserving extinction in clinical samples offers, besides the potential for discerning vulnerability to ADs, the possibility to predict treatment response, and to derive implications for treatment itself (Craske et al., 2018).

4.2. Exposure therapy as first-line treatment for anxiety disorders

Cognitive behavioral therapy (CBT) subsumes a class of interventions based on the assumption that cognitive factors are responsible for maintaining emotional disorders and that these factors are changed through psychological treatment using cognitive (e.g. cognitive restructuring, psychoeducation) and behavioral (e.g., exposure, relaxation training, social skills training) techniques (Beck, Emery, & Greenberg, 2005).

Exposure-based CBT as the first-line treatment for ADs (Bandelow et al., 2014) includes the repeated confrontation and the systematical approaching (instead of avoiding) to feared stimuli in absence of the feared outcome. This procedure is analog to fear extinction, where the CS, which has been previously paired with an aversive US, is then repeatedly presented without the US. Exposure therapy is ergo a successful example of the intertwining of basic research and clinical application (Craske et al., 2018).

Exposure-based CBT has proven to be most effective for several ADs in various meta-analyses, yielding large effect sizes for adult and childhood ADs (Butler, Chapman, Forman, & Beck, 2006; Stewart & Chambless, 2009). Evidence suggests that extinction is the central core mechanism underlying fear reduction (Milad & Quirk, 2012; Vervliet et al., 2013), although it still remains intricate to distinctly determine the factors promoting change and the associated therapeutically induced processes leading to change (Heinig et al., 2017).

Despite showing large effect sizes, CBT is not universally efficacious: There are patients unable to complete treatment, and of those who complete, many fail to show clinically significant improvement (Taylor, Abramowitz, & McKay, 2012). Overall treatment response rates for ADs average 49.5% at post-treatment and 53.6% at follow-up, and 40 - 47% show no remission or relapse after successful treatment completion (Loerinc et al., 2015). Average dropout rate for CBT across mental disorders is 15.9% at pre-treatment and 26.2% during treatment (E. Fernandez, Salem, Swift, & Ramtahal, 2015), attrition rates for ADs range between 16 - 31% (E. Fernandez et al., 2015; Taylor et al., 2012).

Thus, although the benefits of exposure-based procedures for ADs are substantial, they´re not stable for everyone. Regrettably, these interventions are often followed by relapse

of symptoms, even after initial successful treatment (de Jong et al., 2019; Thompson, McEvoy, & Lipp, 2018). Hence, a considerable portion of patients may be left as non-responders towards a first-line standard treatment with severe consequences for patients and societies. These figures emphasize the pressing need for intensified research efforts for a better understanding of the mechanisms of exposure-based CBT and for the identification of markers moderating treatment (non-)response (Holmes et al., 2014).

4.3. Moderators of treatment response in anxiety disorders

Evaluating treatment response means that the patient's condition is assessed at baseline and after a fixed duration of treatment in a scientific manner. Treatment response is influenced by several factors like the patient´s personality, the persistence of triggering factors, a concomitant somatic illness, as well as motivational and environmental factors. Besides that, improvement in objective and subjective parameters show different courses. For example, whereas biological parameters might improve, the patient's subjective perception and feelings may remain unchanged, or respectively, improve later than the apparent remission of the disorder. Because clinical improvement occurs in consecutive stages, the following points should be considered when evaluating treatment response. First, (neuro-)biological or neuroimaging parameters may be adequate for validating immediate treatment effects. Second, symptom rating or global functioning scales may assess changes in the patient's subjective experience later (Macher & Crocq, 2004) .

Treatment response means that the a priori defined therapeutic targets were significantly modified by treatment. For rating scales, a reduction in the initial score is defined as significant improvement. Changes below that threshold are then considered as non-response or insufficient response. The main purpose of classifying responders and non-responders to treatment is the identification of patient groups who share similar clinical features (Macher & Crocq, 2004). Non-response, mostly defined as the failure to achieve clinically significant symptom reductions from pre- to post-treatment, describes individuals who might have shown some degree of symptom reduction, but either failed to attain clinically significant improvement or failed to respond to treatment to such an extent that, at the end of treatment, target symptoms showed still clinical significance (Taylor et al., 2012).

However, there are neither standardized approaches for defining treatment response nor for calculating response rates, i.e. the percentage of patients classified as responders (Loerinc et al., 2015). Furthermore, the operationalization of responder status, the number and modality of included measures, and cut-offs to define (non-)response show large variations (Kazdin,

2014; Loerinc et al., 2015). One must keep that in mind when interpreting findings from different studies.

For a long time, it was thought that the biological mechanisms underlying psychotherapeutic actions were not amenable to neurobiological investigation. Thanks to neuroimaging techniques with high spatial and temporal resolution, examining the biological consequences of psychotherapeutic interventions, documenting psychotherapy's effectiveness, and following its course are now possible. The investigation of the biological underpinnings of psychotherapy additionally helps to link specific mental functions with specific brain mechanisms and adds to the knowledge of how the environment affects the brain. Assuming that biological variables cause the behavioral manifestations of mental disorders, these very same should represent more sensitive indices of underlying pathology than monitoring of symptoms. Furthermore, neuroimaging techniques are as well sensitive to both conscious and unconscious processes at the brain-level and can help to conceptualize both psychopathology and psychotherapy (Etkin, Pittenger, Polan, & Kandel, 2005).

Evidence suggests a dual-process model of psychotherapy in ADs, with a decrease in former elevated limbic activation and a concomitant increase in prefrontal activity (Lueken & Hahn, 2016). Knowing that psychotherapy leads to traceable changes at the brain-level, the even more interesting question is, which neural signatures moderating treatment response can be identified already prior to treatment?

A review of neuroimaging studies across ADs suggests that the amygdala, insula, hippocampus, and ACC constitute relevant predictors of treatment response. In addition, abnormalities in hippocampus, amygdala, left middle temporal gyrus (MTG), fusiform gyrus, inferior occipital gyrus (IOG), left transversal temporal gyrus, inferior frontal gyrus (IFG), uncus, and areas associated with emotion regulation (dlPFC, ACC) predict successful outcome of CBT (Santos, Carvalho, Van Ameringen, Nardi, & Freire, 2019).

Another recent cross-diagnostic meta-analysis identified that greater activation in a cluster located in the right cuneus extending into the right superior occipital gyrus (SOG) and right middle occipital gyrus (MOG) was predictive of greater symptomatic improvement in ADs. Psychological therapy in general was associated with reduced activity in the left ACC/paracingulate gyri, the right IFG, and the left IFG/insula after therapy compared to before (Marwood et al., 2018).

Lueken and colleagues (2016) reviewed neurobiological markers related to treatment response in ADs and identified the function of the ACC and the temporal lobe as the most promising markers. However, results were inconsistent regarding the ACC, reporting both

increased and decreased pre-treatment activity as being predictive of better treatment outcome. Clusters found in the temporal lobe encompassing early visual processing (ventral stream) within the temporo-occipital junction may be predictive for treatment outcome, representing neural substrates of visual object processing and recognition. Evidence for other fear-relevant regions like insula, amygdala, mPFC, or occipital lobe showed more null than positive findings.

In a cross-diagnostic study on brain-structural predictors of treatment response, greater pre-treatment volume in the bilateral nucleus accumbens was associated with a greater reduction of anxiety symptoms (clinician-rated) from pre to post CBT. Contrary to expectations, amygdala or vmPFC volume had no predictive value (Burkhouse et al., 2020). In a disorder-specific study, increased right hippocampal volume and increased pre-treatment activation in the insula and the dlPFC during threat processing were predictive for improved outcome in brief CBT in PD patients (Reinecke, Thilo, Filippini, Croft, & Harmer, 2014).

Regarding social anxiety disorder (SAD), occipitotemporal brain activation during the presentation of angry vs. neutral faces was positively associated with response to CBT (Doehrmann et al., 2013). Additionally, greater pre-treatment amygdala activity to threat cues foretold better treatment response in SAD. However, reversed results were found in another study, with less pre-treatment amygdala activity corresponding with greater symptom improvement (Klumpp & Fitzgerald, 2018). Larger resting-state amygdala connectivity to a cluster encompassing the subgenual ACC, caudate, and putamen; and lower amygdala connectivity with a cluster including the bilateral central sulcus and right temporal-occipital regions, predicted enhanced response to CBT in patients with SAD (Whitfield-Gabrieli et al., 2016). Concerning functional connectivity, long-term treatment outcome to internet-delivered CBT in SAD was predicted by less pre-treatment coupling between the amygdala and the dACC to threat. Amygdala activity together with dACC activity to threat significantly distinguished responders from non-responders using support vector machines (Månsson et al., 2015).

One has to bear in mind while interpreting these findings that a brain region may be predictive of treatment outcome in a differential way due to different diagnoses or treatment approaches. Vice versa, another brain region may be a more general predictor of the likelihood of treatment response itself. For example, evidence suggests that differences in emotion regulation mediated via the mPFC may constitute a predictor of treatment response, independent of disorder or treatment approach (Etkin, 2010). In addition, differences in structures and activation patterns suggest that neuroimaging predictors are task dependent, ergo depending on the circuit probed by a paradigm, the stimuli used, and methodological factors (Klumpp & Fitzgerald, 2018).

In general, most studies use neural measures only in sense of a pre- to post-treatment sequence of events, but do not assess the moderating influence and predictive value of pre-treatment neural signatures on treatment outcome. This approach does not allow for identifying moderating or predictive factors already a priori. Hence, studies examining moderating factors of treatment response are still scarce and those studies available, often report inconsistent or even contradictory results.

5. Research questions

The current thesis follows the translational perspective that ADs are developed, maintained, and treated via fear conditioning and extinction processes, as outlined in the introduction. A hyper-conditionability in ADs might lead to the acquisition of abnormally strong associations, which are more resistant to extinction. Extinction learning itself also seems to be impaired in most ADs. Despite abundant research in the last years, aberrant fear conditioning and extinction processes in the ADs are still not fully clear yet, neither transdiagnostically, nor disorder-specific.

Extinction learning is considered a key mechanism of exposure therapy, a first-line treatment for ADs. Although exposure therapy is efficacious, rates of non-responders and relapse rates remain high. There is a pressing need to further improve treatment by investigating the urging question, why some individuals do benefit from treatment while others do not. Research on pre-treatment factors moderating treatment response is therefore of high importance, however, results are still scarce. Knowing in advance who will benefit from treatment or not, could help to personalize therapy, to stratify patients, and to shed additional light on the mechanisms of action related to effective treatment.

Extinction recall, i.e. the long-term retention of extinction learning, represents the final aim of exposure treatment. Due to its high translational value, laboratory assessment of extinction recall in ADs could help in better understanding the problem of clinical relapse and how to prevent it. However, in most human studies (in contrast to animal studies), extinction recall is not assessed explicitly or with inadequate study designs.

The present thesis aimed to address these gaps in current research of ADs by means of two application examples from multicenter trials. The first study employed a novel 3-day fear conditioning, extinction, and extinction recall design, separated by distinct overnight consolidation phases. The aim was to closer match fear conditioning and extinction protocols based on animal research to the clinical level by including extinction recall on a separate day.

The main research question was: Which neural signatures characterize aberrant emotional-associative learning processes - especially extinction recall - in PD compared to HC?

The second study investigated a clinical sample of spider phobia patients undergoing behavioral exposure, ergo addressing extinction as key principle of exposure treatment. The aim was to identify pre-treatment neural moderators of later behavioral exposure outcome using functional activation patterns, functional connectivity, and brain structure. The main research question was: Are there neural signatures prior to treatment, which distinguish between later on responders and non-responders?

II. CHARACTERIZING THE NATURE OF EMOTIONAL-ASSOCIATIVE LEARNING DEFICITS IN PANIC DISORDER

1. Introduction

Emotional-associative learning serves as a translational model for the development, maintenance, and treatment of ADs (Mineka & Oehlberg, 2008) as it represents a key paradigm for understanding the neurobiology of fear and the mechanisms underlying variations in fear memory strength (Johnson, McGuire, Lazarus, & Palmer, 2012). Extinction training, the laboratory analogue to behavioral exposure (Bouton et al., 2001), is currently conceptualized as forming a new memory trace which confers the inhibition of the formerly learned fear reaction when the extinction memory is recalled (Milad & Quirk, 2002). Although extinction has been extensively studied in animals, less is known about alterations in extinction training and recall in ADs. Of note, most studies used one-session fear conditioning and extinction protocols neither allowing for memory consolidation nor for assessing extinction recall – a phenomenon with high translational value for better understanding the problem of clinical relapse.

Fear conditioning enables the organism to avoid future threats in that important information (CS) signaling a potential threat (US) elicits defensive reactions (CR). During fear extinction training, a second fear-inhibitory learning process is initiated, resulting - after successful consolidation - in two memory traces existing in parallel: the conditioning memory (CS-US) and the extinction memory (CS-no-US). When encountering the CS after extinction training, both memory traces can be activated, with the magnitude of fear reactions being dependent on the extent to which the extinction memory is activated (Milad et al., 2006).

The neurophysiology of fear acquisition is well identified (Maren & Quirk, 2004) and highlights the role of the amygdala as central structure for the acquisition and expression of learned fear in rodents (Duvarci & Pare, 2014; LeDoux, 2000) and humans (Phelps et al., 2004; Sehlmeyer et al., 2009). Animal and human neuroimaging studies have also shown overlapping neural systems involved in extinction learning, corroborating the role of the amygdala and the IL cortex in rodents, or respectively, the vmPFC as its human homologue (Delgado et al., 2008; Milad et al., 2014). In comparison to the acquisition, amygdala activity decreases as extinction proceeds while activity in the IL/vmPFC relatively increases (Milad, Wright, et al., 2007) throughout extinction learning as the IL/vmPFC projects to inhibitory neurons within the amygdala (Milad & Quirk, 2012). The IL/vmPFC also constitutes a key region for extinction recall (Davis, 1992; Milad & Quirk, 2002) just as the hippocampus, indicating the importance

of contextual information for retaining extinction memory (Kalisch et al., 2006; Milad, Wright, et al., 2007).

Fear conditioning seems to play a pivotal role for the development and maintenance of PD, although the exact nature of the underlying fear learning and extinction deficits remains under debate (Duits et al., 2015; Lueken et al., 2014). Gorman and colleagues (2000, 1989) presented a neuroanatomical hypothesis according to which the behavioral symptoms of PD are mediated via a neural network encompassing the amygdala, thalamus, hypothalamus, hippocampus, PAG, and locus coeruleus. Accordingly, PD patients are thought to have an abnormally sensitive fear network with lowered activation thresholds resulting in excessive activation. Threat cues can then trigger defensive behavior by activating survival circuits in the brain, probably mediated by the PAG (Hamm, Richter, & Pane-Farre, 2014). To date, several neuroimaging studies have corroborated the pivotal role of certain neural networks for PD pathophysiology (Dresler et al., 2013; Graeff & Del-Ben, 2008; Lueken et al., 2014; Sobanski & Wagner, 2017).

Recent functional studies suggest aberrant activation in an extended network comprising the brainstem, insula, anterior and midcingulate cortices, as well as medial and lateral parts of the PFC in PD (Sobanski & Wagner, 2017). Additional pathophysiological models of PD encompass, among others, interoceptive conditioning processes (e.g. Benke et al., 2018; Bouton et al., 2001; Khalsa and Lapidus, 2016; Pappens et al., 2015) or suffocation false alarm theory (Klein, 1993) resulting in CO_2 hypersensitivity (Esquivel, Schruers, Maddock, Colasanti, & Griez, 2010; Leibold et al., 2016), pointing towards the relevance of brain systems beyond fear conditioning circuits such as the PAG and brainstem (Goossens et al., 2014; Wemmie, 2011). Regarding fear conditioning and extinction, altered neural processing of safety cues (Kircher et al., 2013; Tuescher et al., 2011), a proclivity towards fear overgeneralization (Lissek et al., 2010), or resistance to extinction indicated by a prolonged retention of the CR (Michael, Blechert, Vriends, Margraf, & Wilhelm, 2007) have been considered to be accountable for deviant fear learning processes in PD.

Previous research on fear conditioning and extinction as a pathophysiological marker of PD is however limited by two major shortcomings: First, fear acquisition and extinction are usually conducted within one session (Milad, Wright, et al., 2007) thus not allowing the fear and extinction memory to consolidate. Consequently, alterations pertaining to extinction training of one-session paradigms cannot be unequivocally interpreted as truly representing fear inhibitory learning, but rather a mixture resulting from the recall of the fear memory and the extinction process. Second, the recall of extinction memories is rarely tested at all (as compared

to animal studies that typically include testing on a separate day). Therefore, knowledge about deficits in extinction recall as a correlate of PD is virtually not available, limiting the translation of animal findings to the patient level. From a clinical perspective, it is however essential to test whether patients recall their extinction memories, i.e. actively inhibit fear reactions, when encountering the CS again. The phenomenon of relapse after successful behavioral exposure frequently seen in ADs (Taylor et al., 2012) could thus be interpreted as a failure to consolidate or recall extinction memories.

Following this translational perspective, the present study aimed to closer match fear conditioning and extinction protocols based on animal research to the clinical level. Investigating the neural substrates of fear conditioning, extinction training, and recall separated by distinct overnight consolidation phases, we applied a three-day fear conditioning and delayed extinction paradigm.

Regarding the acquisition of newly conditioned fears during day 1, we expected patients to show heightened activity in defensive networks encompassing the amygdala and insula as an indicator of exaggerated conditionability (Mineka & Oehlberg, 2008; Phelps et al., 2004). Second, when recalling the fear conditioning memories at the beginning of day 2, we expected patients to show stronger activation of these networks compared to controls. After completion of the extinction training and following overnight consolidation, we hypothesized patients will show impaired recall of the extinction memory on day 3 as represented by stronger and prolonged activation of defensive networks compared to controls, where fear inhibition should take place faster.

2. Methods

2.1. Inclusion criteria and recruitment pathway

As part of the multicenter national research network "Panic-Net" (Federal Ministry of Education and Research – BMBF, 2nd funding period) a total of n = 20 quality-controlled datasets with full data from all three days were included in this analysis, consisting of n = 10 patients with PD and n = 10 HC. Patients were recruited from the psychotherapy outpatient center at Technische Universität Dresden; HC responded to local advertisements. Patients and controls were matched for age, gender, smoking status, handedness (only right-handers), and educational level.

Patient inclusion criteria comprised a primary diagnosis of PD according to DSM-IV-TR criteria (American Psychiatric Association, 2000), age between 18-65 years, and a score ≥ 4 at the Clinical Global Impressions Scale (CGI; Guy, 1976). Patients completed the

Panic and Agoraphobia Scale (PAS; Bandelow, 1999), Anxiety Sensitivity Index (ASI; Reiss et al., 1986), and the Beck Depression Inventory (BDI; Beck et al., 1961). Overall anxiety severity was rated by trained clinicians using the Structured Interview Guide for the Hamilton Anxiety Scale (SIGH-A; Shear et al., 2001).

Exclusion criteria encompassed suicidal intent, psychotic and bipolar disorders, borderline personality disorder, substance dependency, ongoing treatment, antidepressant or anxiolytic pharmacotherapy, or any medical disease that could account for patients´ symptoms. All other comorbidities including unipolar depression and further ADs were allowed as long as they were not of primary clinical concern. HC were free of past or current psychiatric, neurological or medical illness. Pregnancy and magnetic resonance imaging (MRI)-related contraindications were general exclusion criteria for both groups.

Sample characteristics were analyzed using χ^2 and *t*-tests as implemented in SPSS 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) with $p < 0.05$ serving as a statistical threshold. After receiving a detailed description of the study, participants provided informed written consent. The study was approved by the ethics committee of the Technische Universität Dresden (EK 62022010).

2.2. Overview of study protocol

A differential fear conditioning and delayed extinction paradigm for functional MRI (fMRI) was conducted on three consecutive days (habituation & fear acquisition on day 1; extinction training on day 2; extinction recall on day 3; see figure 2 for details). In addition to the fear conditioning procedure on day 1, participants completed a semantic priming task (Yang et al., 2016) and an agoraphobia symptom provocation task ("Westphal paradigm", Wittmann et al., 2011). Two neutral pictures of male faces (Ekman faces, Ekman, 1992) served as CSs with a reinforcement rate of 100%, while an aversive panic scream (2s, 95 dB, calibrated with an artificial ear) served as auditory US. Assignment of the faces as CS+ or CS- was counterbalanced and stimuli were presented in a pseudorandomized order (max. of two repetitions of each stimulus). A jittered inter-stimulus-interval between 7.7 - 16.2 s was used after each trial to allow for the assessment of skin conductance responses (SCRs) within a time window of 1 - 5 s after stimulus offset.

Every experimental phase consisted of 8 presentations of each CS (and during acquisition, the US, respectively). The entire paradigm consisted of nine experimental phases allowing for sufficient time resolution for the respective learning and recall phases [day 1: habituation (H), early and late acquisition (A1, A2); day 2: recall CR (ET1), early and late extinction training (ET2, ET3); day 3: return of fear (ER1), early and late extinction recall (ER2,

ER3); duration at each day approx. 15 min]. Online-recordings of stimulus-specific SCRs and subjective valence and arousal ratings were collected as indicators of successful conditioning and contingency knowledge.

Ratings were assessed after each phase using a nine-point Likert scale for both CSs (for valence: 1, ‘very positive’ to 9 ‘very negative’; for arousal: 1, ‘very low’ to 9 ‘very high’), presented in counterbalanced order. Stimuli were presented via MR-compatible LCD goggles and headphones using Presentation 14 (Neurobehavioral Systems; www.neurobs.de). Awareness of the CS-US contingency was assessed in a post-experimental interview (see appendix for details).

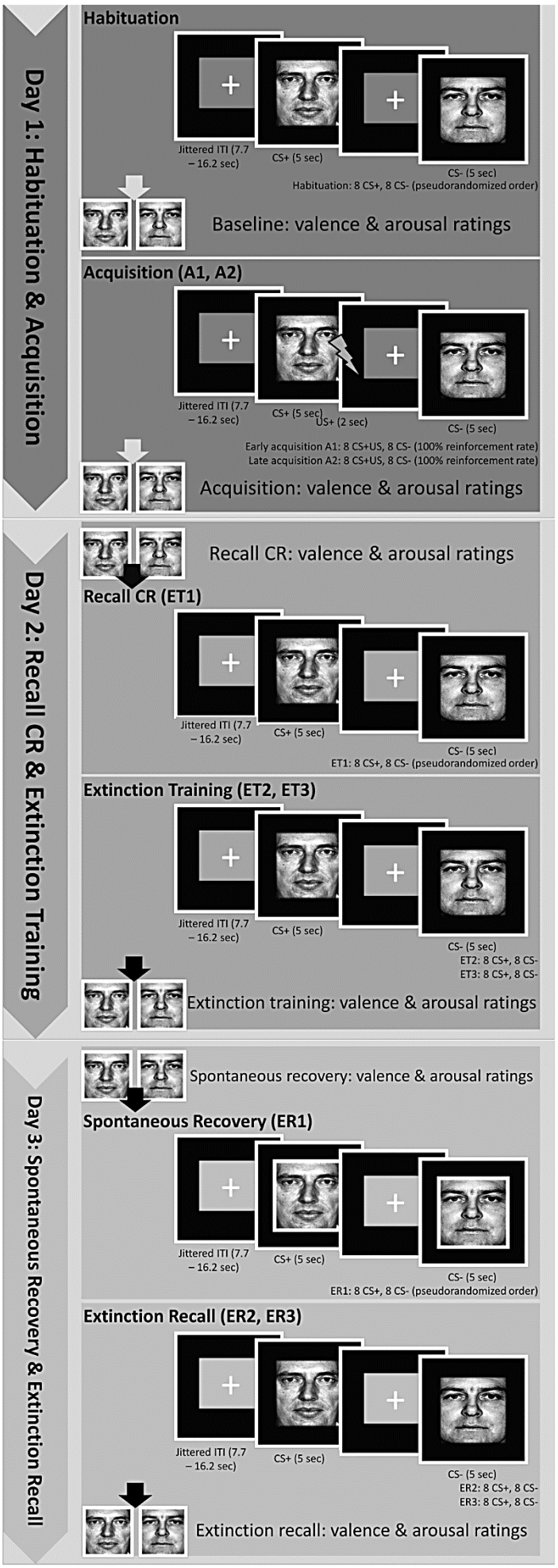

Figure 2. Differential fear conditioning and delayed extinction task. Day 1: habituation & acquisition (A1, A2); day 2: recall conditioned response (CR) after overnight consolidation (ET1) and extinction training (ET2, ET3); day 3: return of fear (ER1) and extinction recall after overnight consolidation (ER2, ER3). CS+: conditioned stimulus (CS) paired with the US. CS-: CS never paired with the US. ITI: intertrial interval; US: unconditioned stimulus (human panic scream).

2.3. fMRI data acquisition and analysis

MRI images were acquired on a 3-Tesla Trio-Tim MRI whole-body scanner (Siemens, Erlangen, Germany). On day 1, 368, and on day 2 and 3, 356 axial functional images [echo-planar imaging (EPI): matrix 64x64, 41 slices interleaved (bottom-up), field of view (FOV) = 192, voxel size = 3x3x3mm, echo time (TE) = 25ms, repetition time (TR) = 2.5s] covering the whole brain were acquired using a tilted angle of 20° to the anterior – posterior commissure (AC-PC) to reduce susceptibility artifacts in inferior brain areas (Deichmann, Gottfried, Hutton, & Turner, 2003). In addition, a structural data set [magnetization prepared rapid gradient echo (MPRAGE): matrix = 256x256, slices = 176, FOV = 256, voxel size = 1x1x1mm, TE = 2.26ms, TR = 1.9s, flip angle = 9°] was recorded. The 5 initial scans were discarded to avoid T1 saturation effects.

Data analyses were carried out using Statistical Parametric Mapping (SPM8; www.fil.ion.ucl.ac.uk/spm/software/spm8/) implemented in MATLAB®R2012a (Mathworks Inc., USA.), applying a high-pass filter (cutoff period, 128 seconds) to remove low-frequency fluctuations in the blood-oxygen-level-dependent (BOLD) signal. Functional images were preprocessed, encompassing slice time correction to correct for differences in image acquisition time between slices, realigned and unwarped to correct for movement artifacts. We coregistered T1 and EPI images, segmented the coregistered T1 images and normalized EPI images (3x3x3mm resolution) using T1 segmentation maps into standard stereotactic space [Montreal Neurologic Institute (MNI) template; 3x3x3mm]. Normalized EPI data were smoothed with a Gaussian kernel of 6 mm FWHM (full-width at half-maximum).

First-level statistical analysis was done for all subjects applying the general linear model (GLM). Using an event-related design, realignment parameters and rating phases were included as regressors of no interest. The BOLD response was modelled for each event type (CS+, CS-, US) and phase, including each day as a separate session (day 1: H, A1, A2; day 2: ET1, ET2, ET3; day 3: ER1; ER2; ER3) convolved with the canonical hemodynamic response function within the framework of the GLM, resulting in eight regressors of interest on day 1 (HCS+, HCS-, A1CS+, A1CS- A1US, A2CS+, A2CS-, A2US), and six regressors of interest on day 2 and 3 (day 2: ET1CS+, ET1CS-, ET2CS+, ET2CS-, ET3CS+, ET3CS-; day 3: ER1CS+, ER1CS-, ER2CS+, ER2CS-, ER3CS+, ER3CS-).

Parameter estimates (beta values) and *t*-statistic images were calculated for each subject. The group analysis was performed by including contrast images into a full factorial analysis. As patients and controls were well matched, no additional covariates were included. Contrasts

of interest (*t*-contrasts) were computed separately for each full phase (e.g. acquisition) and its subphases (e.g. A1, A2).

In a first step we investigated the main task effects on differential conditioning (CS+ > CS-) in the entire group (A: CS+ > CS-; A1: CS+ > CS-; A2: CS+ > CS-; ET: CS+ > CS-; ET1: CS+ > CS-; ET2: CS+ > CS-; ET3: CS+ > CS-; ER: CS+ > CS-; ER1: CS+ > CS-; ER2: CS+ > CS-; ER3: CS+ > CS-). In a second step, we tested for group differences (PD > HC; HC > PD) in these respective contrasts.

As we used this novel paradigm for the first time, exploratory whole-brain results are reported to allow for better comparability with future studies on delayed extinction training and recall. Due to the small sample size and limited statistical power, a liberal significance threshold of $p < 0.005$ uncorrected with a cluster size of $k_E = 15$ voxels was conducted, using the automated anatomical labelling atlas (AAL; Tzourio-Mazoyer et al., 2002) for cluster identification. Beta values from significantly activated brain clusters were extracted using a 5mm sphere and used for bar graph visualization.

2.4. Subjective ratings

Subjective ratings as indicators of contingency knowledge were recorded after H (used as baseline values), A2 (indicating differential fear conditioning), prior to ET1 (ET-pre; indicating recall of CR after consolidation), following ET3 (ET-post; indicating extinction training effects), prior to ER1 (ER-pre; indicating return of fear), and after completion of ER3 (ER-post; indicating extinction recall). A three-factorial repeated-measures Analysis of Variance (ANOVA) as implemented in SPSS 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.) with the two within-subject factors “phase” (H, A, ET1, ET3, ER1, ER3) , “CS-type” (CS+, CS-), and the between-subject factor “group” (PD, HC) was used to test for main and interaction effects, followed by pairwise comparisons to localize the direction of effects.

2.5. SCR data acquisition and analysis

SCRs were recorded during scanning with Ag/AgCl electrodes (MES Medizintechnik, Munich, Germany) attached to the second phalanx of the index and middle finger of the non-dominant hand, using isotonic electrode paste as contact medium (Synapse, Kustomer Kinetics, Arcadia, CA, USA) and Brain Vision hard- and software for data acquisition (Brain Vision ExG Amplifier and Brain Vision Recorder; Brain Products, Munich, Germany). Data were recorded with an initial sampling rate of 1000 Hz (downsampled to 10 Hz), applying a low cut-off filter of 10 s and a high cut-off filter of 250 Hz. A Matlab based application (Ledalab Version 3.3.4,

Benedek and Kaernbach, 2010) was employed to run a discrete decomposition analysis from which through-to-peak values were used to calculate the sum amplitude of the first interval response (FIR) within a time window of 1 - 5 s after stimulus offset (response criterion 0.02 μS). SCR data were range-corrected according to Lykken (1972). A three-factorial repeated ANOVA employing the factors "group", "CS" and "phase" (H1 H2, A1, A2, ET1, ET2, ET3, ER1, ER2, ER3) was employed. Due to technical failure, SCR datasets from one patient and one HC were missing for day 3. If sphericity assumptions were not met, Greenhouse-Geisser corrections were applied, $p < 0.05$ indicated statistical significance

3. Results

3.1. Sample characteristics

Sample characteristics are given in table 1.

Table 1. Demographic and clinical sample characteristics for PD patients and healthy controls (N = 20).

	patients (n = 10)	controls (n = 10)	χ^2 or t (df)	p
Demographic characteristics				
Age (years)	27.5 (8.5)	27.6 (8.0)	0.027 (18)	0.979
Female gender [n (%)]	7 (70)	7 (70)	0.00 (1)	1.00
Right-handed [n (%)][a]	10 (100)	10 (100)	0.00 (1)	1.00
Smoker [n (%)][b]	3 (30)	2 (20)	0.148 (1)	0.701
Education [n (%)]			0.267 (1)	0.606
10 years	3 (30)	2 (20)		
12 - 13 years	7 (70)	8 (80)		
Clinical characteristics				
CGI	4.3 (0.63)	-	-	-
PAS	20.0 (6.73)	-	-	-
SIGH-A	15.6 (6.75)	2.2 (2.39)	-5.91 (11.23)	<0.001
ASI	35.4 (10.1)	8.7 (5.12)	-7.44 (18)	<0.001
BDI-II	10.9 (5.36)	1.1 (1.85)	-5.46 (11.12)	<0.001

PD: panic disorder; CGI: Clinical Global Impression; PAS: Panic and Agoraphobia Scale; SIGH-A: Structured Interview Guide for the Hamilton Anxiety Scale; ASI: Anxiety Sensitivity Index; BDI-II: Beck Depression Inventory II

[a] available for n = 19; [b] available for n = 19

Values given as mean (standard deviation) except where noted.

3.2. Behavioral indicators of conditioning

Information on contingency awareness can be found in the supplemental results in the appendix. Briefly, we observed a main effect of conditioning in arousal ratings in the entire group, but no differences between patients and controls.

3.2.1. Valence

A significant main effect of phase was found for CS-valence ratings (F (5, 90) = 4.190, p = 0.002). Valence was rated significantly more negative after the acquisition phase than after the habituation (F (1, 18) = 5.434, p = 0.032) and prior to extinction recall (F (1, 18) = 5.630, p = 0.028). After extinction recall, valence was rated significantly more positive than in all other phases (all $p < 0.05$). No further significant main or interaction effects on valence ratings could be observed (main effect group: F (1,18) = 0.027, p = 0.871, main effect CS: F (1,18) = 1.945 , p = 0.180 , interaction effect CS x group: F (1,18) = 0.182, p = 0.675 , interaction effect CS x phase: F (2.72,49) = 1.989 , p = 0.133 , interaction effect phase x group: F (5,90) = 0.660, p = 0.654, interaction effect CS x phase x group: F (5,90) = 0.470 , p = 0.798; see figure 3).

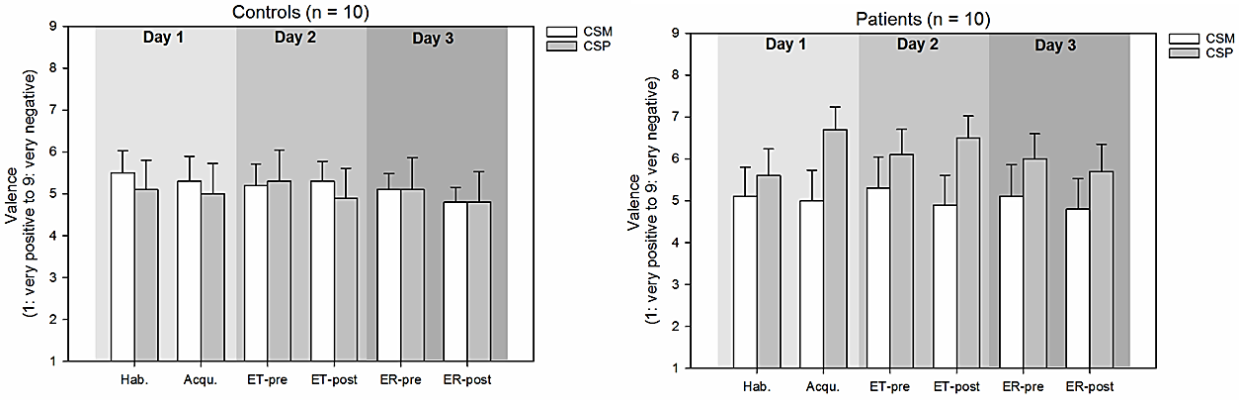

Figure 3. Subjective valence ratings of the delayed fear extinction task. Healthy controls (left) and patients (right). Error bars indicate the standard error of means (SEM). No main or interaction effects for CS-type or group were observed.

3.2.2. Arousal

We observed a significant interaction of phase and CS-type (F (2.41, 43.38) = 6.752, p = 0.002) indicating successful fear conditioning in the entire group (see figure 4). The CS+ was rated as significantly more arousing than the CS- following the acquisition (z = 2.315, p = 0.021) and after extinction training (z = 2.032, p = 0.042). Furthermore, a significant main effect of phase was found (F (5, 90) = 4.075, p = 0.002). We observed higher arousal ratings following acquisition than after extinction training (F (1, 19) = 5.627, p = 0.028) as well as higher arousal ratings in all phases compared to arousal after extinction recall (all $p < .05$). All other effects

were not significant (main effect CS: F (1, 18) = 3.210, p = 0.090, main effect group: F (1, 18) = 0.114, p = 0.739, interaction effect CS x group: F (1, 18) = 0.058, p = 0.090, interaction effect group x phase: F (5, 90) = 0.599, p = 0.701).

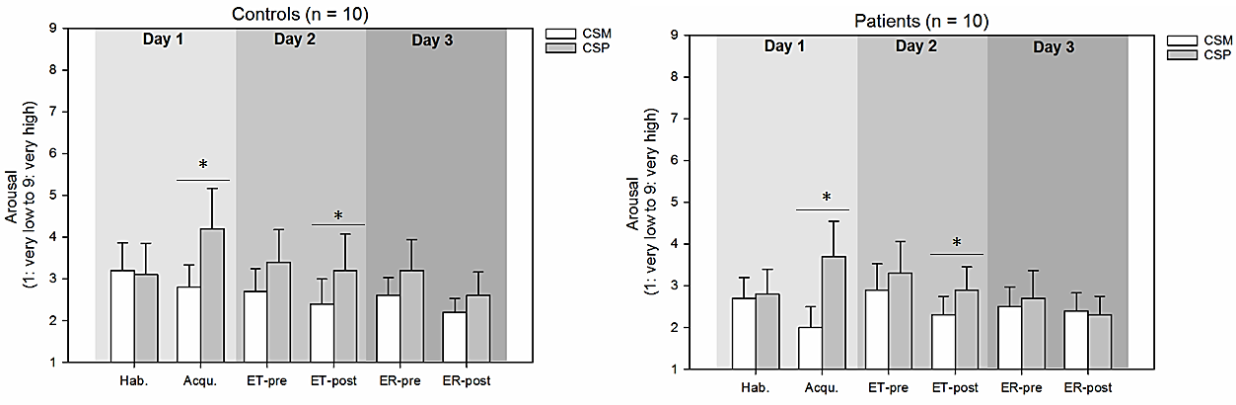

Figure 4. Subjective arousal ratings of the delayed fear extinction task. Healthy controls (left) and patients (right). Successful fear conditioning as evidenced by CS*time effect in both groups, while no group effects were observed. Error bars indicate the standard error of the mean (SEM). *p < 0.05.

3.2.3. Skin conductance response (SCR)

No main or interaction effects on SCR were observed (main effect CS: F (1,16) = 2.615 , p = 0.125 , main effect phase: F (3.38,54.11) = 2.017 , p = 0.115, main effect group: F (1,16) = 0.130, p = 0.723, interaction effect phase x CS: F (3.15,50.37) = 1.133, p = 0.346 , interaction effect group x CS: F (1,16) = 2.709 , p = 0.119, interaction effect group x phase: F (3.38,54.11) = 1.684 , p = 0.176, phase x CS x group: F (3.15,50.37) = 1.064, p = 0.375; see figure 5 for details).

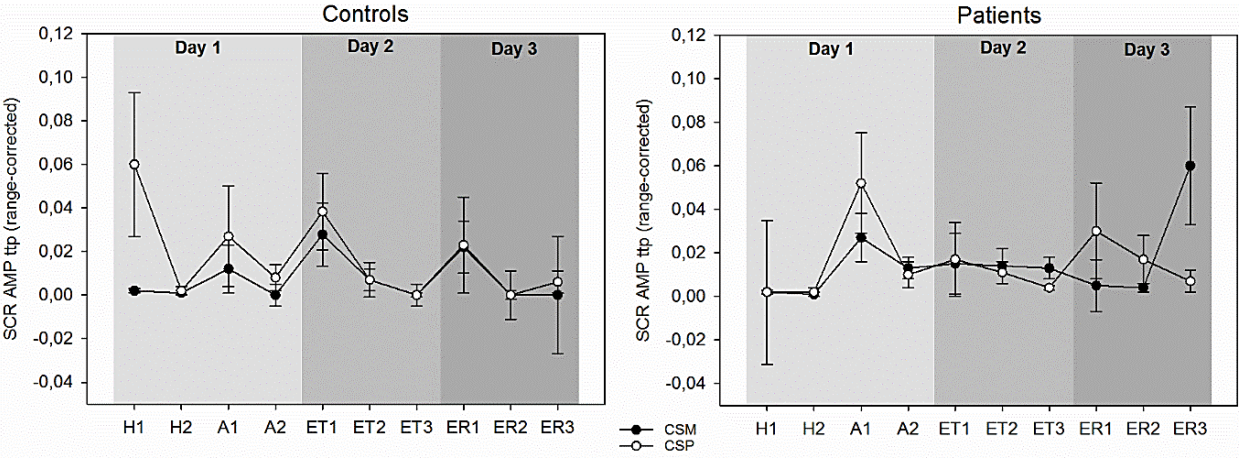

Figure 5. Skin conductance response (SCR) of the delayed fear extinction task. Healthy controls (left) and patients (right). No main or interaction effects were observed. Error bars indicate the standard error of the mean (SEM).

3.3. Differential conditioning and extinction effects in the combined sample

fMRI results for the main task effects are given in table 2 and figure 6. During acquisition we observed, among others, activation in the right SMA, bilateral precentral gyri, and thalamus in response to the CS+ > CS-. The extinction training activated the right thalamus, bilateral superior frontal gyri (SFG), bilateral insular cortices, as well as the left inferior frontal operculum (IFO) and right SMA. These activation patterns were mainly driven by the ET1 phase indicating the recall of the CR. During the early extinction recall on day 3 (ER1), the right angular gyrus, precuneus, left supramarginal gyrus, and inferior parietal lobule showed heightened activation towards the CS+.

Table 2. Brain activation patterns during fear acquisition, extinction and extinction recall to conditioned stimulus (CS+ vs. CS-) for the combined sample.

Contrast/region	side	voxels	x	y	z	t	*p*
Combined Sample							
Full acquisition: ACS+ > ACS-							
Supplementary motor area	R	309	15	2	70	4.73	<0.001
Rolandic operculum	L	123	-33	-28	16	4.28	<0.001
Heschl gyrus	R	62	48	-19	7	4.06	<0.001
Precentral gyrus	L	41	-45	-4	40	3.63	<0.001
Precuneus	R	110	-6	-46	52	3.41	<0.001
Precentral gyrus	R	40	45	-1	46	3.35	<0.001
Early acquisition: A1CS+ > A1CS-							
Supplementary motor area	L	100	-9	5	49	3.77	<0.001
Precentral gyrus	R	16	48	-4	49	3.11	0.001
Late acquisition: A2CS+ > A2CS-							
Parahippocampal gyrus	R	24	6	-13	-20	4.07	<0.001
Supplementary motor area	R	124	12	-1	73	4.01	<0.001
Superior temporal gyrus	R	132	-45	-34	10	3.97	<0.001
Heschl gyrus	R	74	39	-31	16	3.66	<0.001
Precuneus	R	61	6	-52	52	3.54	<0.001
Pallidum	L	44	-12	2	-2	3.38	<0.001
Thalamus	R	25	9	-22	1	3.36	<0.001
Putamen	R	17	18	11	1	3.13	0.001
Full extinction training: ETCS+ > ETCS-							
Thalamus	R	62	15	-13	1	3.88	<0.001
Superior frontal gyrus	R	25	27	44	13	3.86	<0.001
Inferior frontal gyrus	L	85	-36	20	7	3.72	<0.001
Insula	R	109	45	20	1	3.57	<0.001
Middle frontal gyrus	R	24	45	2	55	3.29	0.001
Supplementary motor area	R	39	0	11	55	3.21	0.001
Precentral gyrus	R	39	51	2	34	3.15	0.001

Table 2 (continued).

Early extinction training: ET1CS+ > ET1CS-							
Insula	R	73	33	26	4	3.72	<0.001
Inferior frontal operculum	L	31	-42	14	10	3.63	<0.001
Supplementary motor area	L	28	0	11	55	3.62	<0.001
Insula	L	17	-27	20	4	3.06	0.001
Precentral gyrus	R	27	51	2	37	3.00	0.001
Mid extinction training: ET2CS+ > ET2CS-						no differential activation	
Late extinction training: ET3CS+ > ET3CS-							
Superior frontal gyrus	R	46	30	59	13	3.59	<0.001
Thalamus	L	30	-3	-22	-5	3.32	0.001
Full extinction recall: ERCS+ > ERCS-						no differential activation	
Early extinction recall: ER1CS+ > ER1CS-							
Angular gyrus	R	46	30	-46	40	3.73	<0.001
Supramarginal gyrus	L	32	-54	-28	34	3.52	<0.001
Precuneus	R	23	21	-70	43	3.37	<0.001
Inferior parietal lobule	L	28	-48	37	46	3.00	0.001
Mid extinction recall: ER2CS+ > ER2CS-						no differential activation	
Late extinction recall: ER3CS+ > ER3CS-						no differential activation	

CS: conditioned stimulus; CS+: CS that is followed by an unconditioned stimulus; CS-: CS that is never followed by the US; L: left; R: right; voxel: number of voxels per cluster; x, y, z: MNI coordinates. Whole-brain results at $p < 0.005$ (uncorrected) with a minimum cluster size of $k_E = 15$ contiguous voxels.

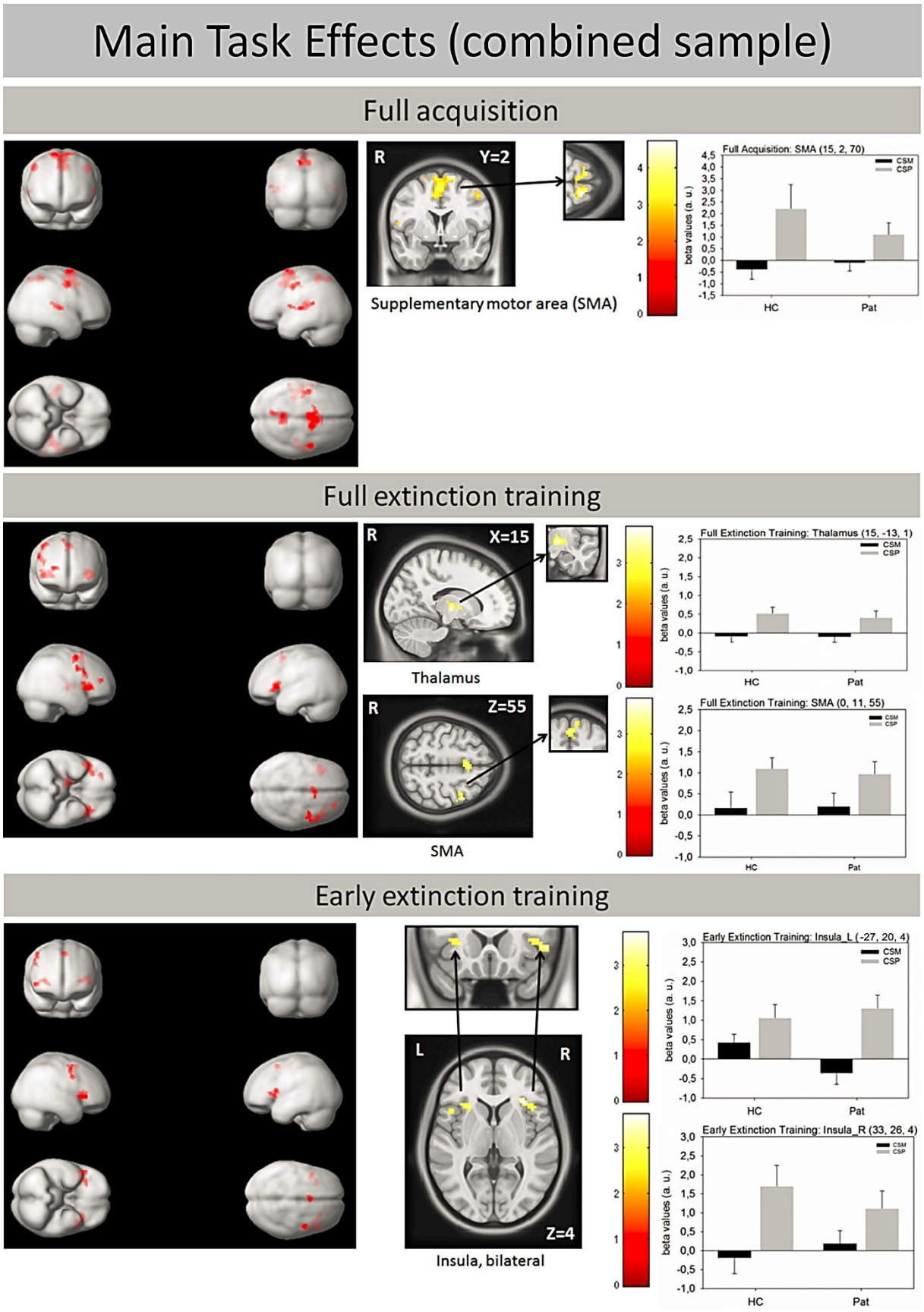

Figure 6. Neural markers of differential fear conditioning for the combined sample for the contrast CS+ > CS-. CS+: conditioned stimulus (CS) followed by the unconditioned stimulus (US); CS-: CS never followed by the US. Error bars indicate the standard error of the mean (SEM).

3.4. Group differences in differential conditioning, extinction training, and recall

During early acquisition, patients exhibited stronger neural activation in the left fusiform gyrus, the right amygdala, and the left insula in response to CS+ > CS- than HC. In turn, HC showed, among others, stronger activation of the right middle frontal gyrus (MFG) towards the CS+. On day 2, HC also showed, among others, enhanced activation in the left MTG, left medial SFG, and in the left midcingulate and SMA (ET1). During early extinction recall on day 3, HC activated the right MFG stronger than patients. On the contrary, patients showed attenuated extinction recall during ER2 and 3 as indicated by stronger activation in the right insula (ER2), left IFO, and the left IFG (ER3) (see table 3 and figure 7).

Table 3. Brain activation patterns during fear acquisition, extinction, and extinction recall to conditioned stimulus (CS+ vs. CS-) for PD patients vs. healthy controls and vice versa.

Contrast/region	side	voxels	x	y	z	t	*p*
Patients > Healthy Controls							
Full acquisition: ACS+ > ACS-							
Hippocampus	R	16	33	-4	-17	3.63	<0.001
Superior temporal gyrus	R	19	45	-4	-11	2.90	0.002
Early acquisition: A1CS+ > A1CS-							
Fusiform gyrus	L	178	-36	-25	-20	3.82	<0.001
Amygdala[1]	R	91	33	-4	-14	3.48	<0.001
Insula	L	16	-30	-13	19	3.30	<0.001
Vermis 4 5		19	-3	-55	-26	3.20	0.001
Cerebellum 6	L	37	-12	-64	-14	3.20	0.001
Late acquisition: A2CS+ > A2CS-						no differential activation	
Full extinction training: ETCS+ > ETCS-						no differential activation	
Early extinction training: ET1CS+ > ET1CS-						no differential activation	
Mid extinction training: ET2CS+ > ET2CS-						no differential activation	
Late extinction training: ET3CS+ > ET3CS-						no differential activation	
Full extinction recall: ERCS+ > ERCS-						no differential activation	
Early extinction recall: ER1CS+ > ER1CS-						no differential activation	
Mid extinction recall: ER2CS+ > ER2CS-							
Insula	R	29	42	5	-5	3.56	<0.001
Late extinction recall: ER3CS+ > ER3CS-							
Inferior frontal operculum	L	19	-42	14	19	3.20	0.001
Inferior frontal gyrus	L	16	-30	41	-2	2.88	0.002

Table 3 (continued).

Healthy Controls > Patients							
Full acquisition: ACS+ > ACS-						no differential activation	
Early acquisition: A1CS+ > A1CS-							
Middle frontal gyrus	R	39	24	29	37	3. 13	0.001
Late acquisition: A2CS+ > A2CS-							
Rolandic operculum	R	233	42	-25	22	4.17	<0.001
Postcentral gyrus	L	146	-42	-19	43	3.82	<0.001
Postcentral gyrus	L	36	-60	-19	22	3.62	<0.001
Postcentral gyrus	L	17	-54	-4	13	3.54	<0.001
Inferior parietal lobule	L	22	-57	-37	46	3.28	0.001
Precentral gyrus	R	21	39	-4	40	3.14	0.001
Full extinction training: ETCS+ > ETCS-							
Middle temporal gyrus	L	35	-54	-34	-14	3.24	0.001
Medial superior frontal gyrus	L	21	-3	29	61	3.19	0.001
Precuneus	L	19	-6	-52	34	3.05	0.001
Early extinction training: ET1CS+ > ET1CS-							
Midcingulate cortex	L	37	-15	2	34	3.94	<0.001
Supplementary motor area	L	38	0	20	64	3.24	0.001
Precuneus	R	18	6	-73	43	3.11	0.001
Supramarginal gyrus	R	20	45	-43	25	2.99	0.001
Mid extinction training: ET2CS+ > ET2CS-						no differential activation	
Late extinction training: ET3CS+ > ET3CS-						no differential activation	
Full extinction recall: ERCS+ > ERCS-						no differential activation	
Early extinction recall: ER1CS+ > ER1CS-							
Supramarginal gyrus	R	15	54	-43	31	3.38	<0.001
Middle frontal gyrus	R	15	39	11	37	3.26	0.001
Mid extinction recall: ER2CS+ > ER2CS-						no differential activation	
Late extinction recall: ER3CS+ > ER3CS-						no differential activation	

[1] cluster encompassing hippocampus and insula

CS: conditioned stimulus; CS+: CS that is followed by an unconditioned stimulus; CS-: CS that is never followed by the US; L: left; R: right; voxel: number of voxels per cluster; x, y, z: MNI coordinates. Whole-brain results at $p < 0.005$ (uncorrected) with a minimum cluster size of $k_E = 15$ contiguous voxels.

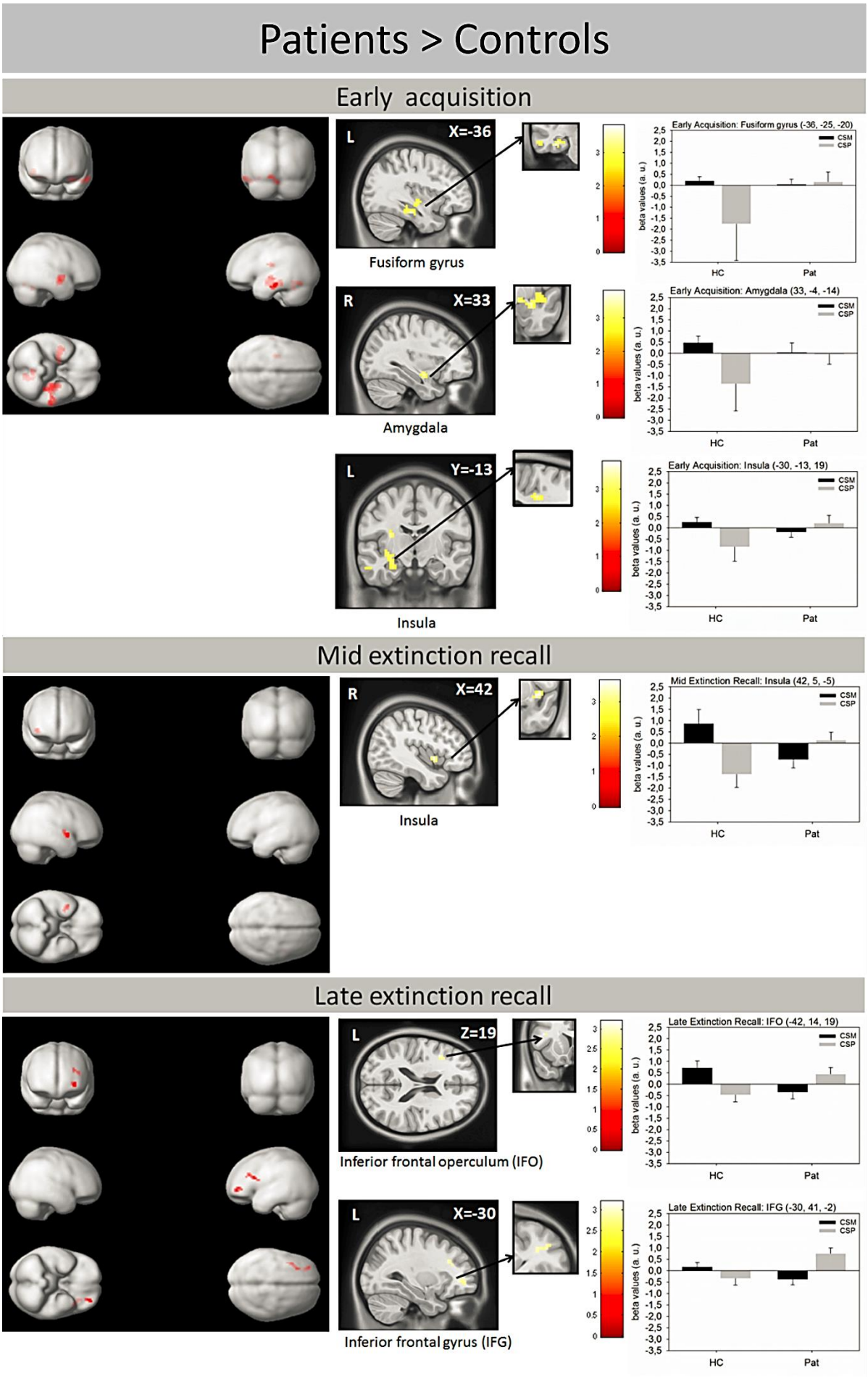

Figure 7. For figure caption, see next page.

Figure 7. Neural markers of differential fear conditioning for PD patients vs. healthy controls. CS+: conditioned stimulus (CS) followed by the unconditioned stimulus (US); CS-: CS never followed by the US. Error bars indicate the standard error of the mean (SEM). PD: panic disorder.

4. Discussion

The present study employed a differential fear conditioning and delayed extinction paradigm on three consecutive days in patients with PD for the purpose of disentangling neural networks involved in fear acquisition, extinction, and recall of fear-related memories to gain more insight into altered patterns of brain activation as a function of PD. Focusing on extinction recall may improve our understanding of how fear-inhibitory learning induced by behavioral exposure may be consolidated and retrieved in patients (Marin, Camprodon, Dougherty, & Milad, 2014).

Two major effects were observed: first, on a neural level, PD patients were characterized by enhanced activation in networks subserving fear conditioning such as the amygdala or insula, particularly during the initial trials of the acquisition phase, possibly indicating accelerated fear conditioning processes as a function of pathophysiology. Second, patients showed attenuated recall of extinction memories as indicated by sustained activation of fear circuitry networks encompassing the insula, IFO, and IFG.

4.1. Neural networks of fear conditioning, extinction training, and recall

In line with expectations, stronger neural activation during day 1 in networks conferring differential fear conditioning such as the SMA, superior temporal gyrus (STG), or thalamus (Fullana et al., 2016; Sehlmeyer et al., 2009) were observed in the entire group, indicating that successful conditioning was induced. Due to power restrictions in this small sample, no effects on autonomic responding were observed, but higher arousal ratings for the CS+ after the fear acquisition phase also supported the conditioning effects. Interestingly, neural activation patterns during day 2 could be mainly traced back to the early extinction phase, which we thought to capture the recall of the overnight consolidated fear conditioning memory trace. Supporting this assumption, we predominantly observed activation in fear circuitry networks such as the bilateral insula, left IFO, and bilateral SMA. The present experimental design explicitly allowed for consolidation of fear conditioning and extinction memories. We conclude that at least the initial trials of fear extinction tasks rather indicate recalling fear memories, than reflecting fear-inhibitory processes yet. These findings emphasize methodological limitations of combined one-session fear conditioning and extinction tasks as previously conducted by the majority of studies in this field.

We were not able to identify clear-cut neural substrates of extinction training in contrast to other neuroimaging studies which suggest an extinction network including the amygdala,

ACC, PCC, insula, and (vm)PFC (Sehlmeyer et al., 2009). Again, power limitations due to the sample size may account for these null-findings: effects of fear conditioning are usually well pronounced and thus detectable in smaller samples, however, this may not refer to extinction processes. Alternatively, the timely dynamics of extinction may vary between subjects, making it difficult to trace them on a group level, although we took temporal dynamics into account using an early and late extinction training phase. Instead, the SFG, which is associated with cognitive control and response inhibition (Boisgueheneuc et al., 2006; Floden & Stuss, 2006) activated stronger during the late extinction training. This finding could imply that increased cognitive control may be gained during extinction training, possibly reflecting alternative (e.g. cognitively mediated) routes of fear inhibition.

For extinction recall during day 3, we found stronger activation in the angular gyrus and the neighboring supramarginal gyrus, as well as the right precuneus. These brain areas are involved in memory retrieval and general attention (Lundstrom, Ingvar, & Petersson, 2005; Seghier, 2013) and enhanced activation may reflect attentional shifts towards the more salient CS+. However, no neural substrates as derived from animal studies encompassing the (v)mPFC (Milad & Quirk, 2002) could be identified as a function of extinction recall.

Although increased, yet unspecific attentional network activation was observed during the initial trials of day 3, no ROF seemed to take place. We assume this null-finding to be a consequence of the relatively higher number of trials used for extinction training during day 2, possibly resulting in a very robust fear inhibition. As results for PD patients do however show, this learning and retrieval gradient may differ as a function of pathophysiology, as reflected by floor effects in controls, but not in patients.

In summary, present findings support the notion of successful conditioning induced by the novel paradigm. Moreover, we were able to disentangle conditioning and extinction processes and show that neural substrates during extinction training (day 2) most likely reflect the recall of conditioned responses. Future studies should focus more strongly on targeting the neural substrates of extinction recall in human samples, which are still not fully understood.

4.2. Altered neural networks of fear conditioning, extinction training, and recall in PD patients

On day 1 we observed differential activation during the first trials of the acquisition in patients vs. HC. While HC initially showed a pronounced deactivation in fear circuitry regions towards the CS+, patients exhibited stronger activation in the left fusiform gyrus, right amygdala, and left insula. We assume that this deactivation in HC might represent a latent inhibition phenomenon (the effect that familiar stimuli take longer to become a CS than new stimuli;

Lubow, 1973) due to the relatively prolonged habituation phase. Likewise, stronger MFG deactivation in patients towards CS+ may reflect a lack of this top-down inhibition.

Differences in neural activation patterns during fear conditioning were predominantly observed in fear circuitry networks: the fusiform gyrus, including the fusiform face area (FFA) is known to play a role in face recognition (Weiner & Zilles, 2016). As both CSs were faces, early recognition of perceptual features from salient stimuli such as the CS+ appeared to be amplified during fear conditioning in PD patients. In line, the amygdala and insula, as key regions conferring fear conditioning (LeDoux, 2000; Sehlmeyer et al., 2009) were recruited in patients to a greater extent. We conclude that these findings may serve as initial evidence for accelerated fear conditioning processes in PD possibly representing either a vulnerability for the development, or a consequence of the disorder. As a vulnerability factor, accelerated emotional-associative learning may lead to a greater sensitivity towards aversive events mediated by a faster and stronger linking of former neutral and aversive cues – making people more prone to develop ADs like PD.

Of note, patients showed no differential activation during extinction training on day 2 unlike we expected. However, HC showed even stronger activation in the left MTG, associated with multimodal semantic processing (Visser, Jefferies, Embleton, & Lambon Ralph, 2012), and the left medial SFG, associated with cognitive control and attention set shift between object features (Nagahama et al., 1999). This could represent a stronger sensory processing of the CS+ in HC.

During extinction recall on day 3, we observed stronger neural responding in the right insula, the left IFO, and the left IFG in patients. These findings point towards deficits in extinction recall rather than training. In contrast, HC showed stronger activation of the right MFG towards the CS+ already during early ER which might reflect a more efficient recall of extinction memory and hence, stronger top-down suppression of CS+ responding (similar to effects during early acquisition). Heightened insular activation during mid extinction recall in patients, on the other hand, is interpreted as attenuated fear inhibition with stronger activation of defensive networks. The left IFG is known to be involved in response inhibition and inhibitory processes in general (Swick, Ashley, & Turken, 2008). Findings may indicate stronger suppression of behavioral tendencies in response towards the (still) fear eliciting CS+ in patients even during the recall of extinction memories. Results support previous findings on the association of increased IFG activation as a feature of fear conditioning in PD (Kircher et al., 2013; Lueken et al., 2014) that was modulated by CBT (Kircher et al., 2013) which is based on the principles of extinction. Laboratory studies show that even if fears are easy to extinguish,

they recover yet more easily, i.e. extinction may be easy to learn but hard to remember (Vervliet et al., 2013).

This raises the question if there is maybe not (only) a deficit in extinction training in PD but –in the long run even more debilitating - in extinction recall, like it has been found to be the case in other ADs like OCD (Milad et al., 2013) and PTSD (Rougemont-Bücking et al., 2011). PTSD can be characterized by pathological fear memories – either in the acquisition of fear memories or as pathologies in the expression of an otherwise normal fear memory (VanElzakker, Dahlgren, Davis, Dubois, & Shin, 2014). This has important implications for the treatment as exposure therapy is thought to instantiate fear-inhibitory memories for long-term recall with a focus on relapse prevention (Vervliet et al., 2013).

Neurostimulatory and neuromodulatory treatments bear potential as neuroscience-informed treatment strategies since they may provide access to basic emotional-associative learning processes and memory circuitries (Ressler & Mayberg, 2007) and could be useful tools for augmenting fear extinction. In the long run, it would be ideal to use these promising methods combined with exposure therapy to promote the formation of a strong memory trace during extinction which would reduce the risk of relapse (Marin et al., 2014). Future studies are however needed as a proof of this hypothesis.

4.3. Limitations

Due to the demanding paradigm requiring three consecutive days, the sample with complete data was rather small, pointing towards limitations in conducting sophisticated experimental designs particularly in vulnerable patient groups. Future studies are nevertheless encouraged to replicate these preliminary results.

Employing a habituation phase can furthermore significantly reduce conditioning-related activations of several characteristic brain regions (Fullana et al., 2016). As such, the finding of accelerated conditionability in patients has to be interpreted within the phenomenon of latent inhibition, which may be attenuated in patients.

Context conditioning within the scanner may have occurred as a neuroimaging environment represents a unique context that cannot be changed during an experimental session (VanElzakker et al., 2014). The MRI-scanner itself can represent a threatening situation for anxiety patients, and those suffering from PD and agoraphobia may be especially sensitive to the stress-eliciting properties of the scanner. However, habituation to the scanner environment is frequently seen in patients and controls (Lueken et al., 2011) and subjective ratings after habituation between patients and controls speak in favor of comparable arousal levels.

Nevertheless, an anxious control group would have been of particular value to investigate the transdiagnostic nature of our findings.

4.4. Conclusions and future directions

The present study supports the notion of aberrant neurofunctional activation patterns during emotional-associative learning in PD patients with particular focus on the rapid acquisition of fear memories and impaired recall of extinction memories. Since laboratory fear extinction learning and recall bears similarities to exposure therapy and clinical relapse, it is of pivotal interest to better understand the underlying mechanisms in order to inform novel treatment approaches.

Nevertheless, taking into account the interoceptive nature of PD, further studies using interoceptive conditioning paradigms are needed to shed additional light on the commonalities and differences between interoceptive and exteroceptive emotional-associative learning in PD patients. Future studies should investigate the predictive value of experimental measures of extinction recall for clinical relapse and its implications for exposure-based therapy since failing to recall extinction memories increases the risk for the ROF and consequently for relapse.

Predicting which patient may be vulnerable for relapse could help in supporting clinical decision making on individually tailored treatment approaches. A better understanding of those mechanisms subserving memory consolidation and recall of fear-inhibitory memories could improve measures against clinical relapse.

III. CHARACTERIZING MODERATORS OF TREATMENT RESPONSE TOWARDS BEHAVIORAL EXPOSURE IN SPIDER PHOBIA

1. Introduction

SP has been frequently used a model disorder for studying abnormal fear (Lipka, Miltner, & Straube, 2011). An advantage in specific phobia from the animal subtype is that fear is circumscribed to one specific animal that can be clearly named, like a spider. This offers a high feasibility for symptom provocation studies, since a fear response can be triggered precisely and reliably in the laboratory setting. Studying animal phobia has turned out to be an effective approach to identify brain regions involved in the pathophysiology of excessive fear. Moreover, animal phobias are very common which is a benefit for sample size and generalizability (Britton, Gold, Deckersbach, & Rauch, 2009).

Theories of SP consider fear conditioning as a central pathogenic and maintaining mechanism of the disorder (Schweckendiek et al., 2011). Single-session (i.e. massed) exposure schedules based on extinction principles have been shown to be effective for treating specific fears and phobias (Andersson et al., 2009; Müller, Kull, Wilhelm, & Michael, 2011; Tsao & Craske, 2000). However, despite showing medium to large effect sizes (Carpenter et al., 2018), about two third of patients does not benefit sufficiently (Loerinc et al., 2015). Therefore, identifying neurobiological pre-treatment factors moderating treatment response could aid in personalizing therapy, sparing ineffective treatments, and improving our understanding of the mechanisms underlying effective treatment (Holmes et al., 2014; Lueken & Hahn, 2016).

There is no clear-cut consistent neuroimaging model for SP (Linares et al., 2014), but individuals suffering from SP seem to have an overreactive defense system (Wendt, Lotze, Weike, Hosten, & Hamm, 2008), based on exaggerated responses in brain regions belonging to the fear network (Schweckendiek et al., 2011). The dysfunction of the amygdala is thought to be the central pathophysiological mechanism underlying SP (Nakataki et al., 2017).

Several studies used anxiety provocation paradigms to identify brain regions, which activate when the phobic individual is experiencing high levels of fear and anxiety, could reveal a brain network comprising, inter alia, the amygdala, insula, thalamus, ACC, orbitofrontal cortex (OFC), (v)mPFC, dlPFC, and visual regions (Del Casale et al., 2012; Dilger et al., 2003; Goossens, Schruers, Peeters, Griez, & Sunaert, 2007; Ipser, Singh, & Stein, 2013; Linares et al., 2012; Peñate et al., 2017; Schienle, Schäfer, Hermann, Rohrmann, & Vaitl, 2007; Schienle, Schäfer, Walter, Stark, & Vaitl, 2005; Schweckendiek et al., 2011; Wendt et al., 2008; Zilverstand, Sorger, Kaemingk, & Goebel, 2017), but also other cortices as well as the

cerebellum seem to be involved in the pathophysiology of SP (Del Casale et al., 2012). Additionally, the bilateral SMA exhibited heightened activation in spider phobics upon exposure to phobogenic pictures (Goossens et al., 2007).

Functional connectivity between the left amygdala and postcentral and precentral gyrus, supramarginal gyrus, MTG, and SOG was enhanced in individuals with spider phobia in response to spider pictures compared to HC. Phobics also demonstrated a significantly stronger connectivity between sensorimotor cortex and left PFC than controls (Wiemer & Pauli, 2016). Functional connectivity between the rostral ACC and the left amygdala was significantly higher in patients with small animal phobia in response to phobia-related words compared to neutral words than in healthy individuals (Britton et al., 2009). Another study found enhanced functional coupling between the right amygdala and the periamygdaloid area, the fusiform gyrus, and motor cortex during watching phobic pictures (Åhs et al., 2009).

An early study on brain morphology showed increased cortical thickness in bilateral insulae, bilateral pregenual ACC, bilateral PCC, and left visual cortical regions in subjects with specific animal phobia compared to healthy subjects (Rauch et al., 2004), however, a later study found cortical thinning of the right ACC in spider phobia (Linares et al., 2014). While one study found smaller amygdala volumes (Fisler et al., 2013), another found increased amygdala volume in spider phobia (Schienle, Wabnegger, & Scharmüller, 2014). In general, structural studies in SP are still scarce and inconsistent, or even contradictory.

Taken together, current neural models for SP emphasize the role of the amygdala and related structures and therefore, overlap much with those of other ADs (American Psychiatric Association, 2013). Nevertheless, findings still show inconsistencies. Exposure therapy as first-line treatment for SP has proven effective, though it is neither as effective nor as well understood as one would desire (Böhnlein et al., 2020). On top of this, there are hardly any studies addressing the moderating influence and predictive value of pre-treatment neuroimaging data a priori, but rather pre-post-comparisons. In the long run, however, clinicians and patients would benefit intensely from identified moderators of treatment outcome before starting a potentially ineffective therapy.

We therefore aimed at identifying pre-treatment moderators characterizing treatment response towards behavioral exposure in virtual reality (VR). Potential moderators were examined based on functional brain activation, task-based functional connectivity, and brain structure using a symptom provocation paradigm in patients with spider phobia.

During the symptom provocation, we expected to find heightened activation in defensive and fear circuitry structures (e.g. amygdala, ACC, insula, hippocampus, SMA,

thalamus) in the whole group of patients based on previous studies in spider phobia as outlined above. Comparing responders to non-responders according to pre-defined outcome criteria, we assumed responders to show altered prefrontal activity in regions associated with top-down regulatory and inhibitory processes (e.g. mPFC, lateral PFC), while non-responders may be characterized by enhanced activity in fear and defensive networks. Assessing functional connectivity of the left amygdala during symptom provocation, we expected to find stronger connectivity to other structures of the defensive system network and areas related to fear processing. Comparing responders to non-responders, we assumed responders to show stronger connectivity with prefrontal regions associated with top-down regulatory and inhibitory processes and non-responders to exhibit stronger connectivity to other fear-relevant structures. Since there are hardly any studies investigating structural aberrations in SP at all, and those available are inconsistent as outlined above, we formulated our hypotheses analogously to those expected for functional data.

2. Methods

2.1. Inclusion criteria and recruitment pathway

This clinical study was part of the Transregional Collaborative Research Centre (CRC-TRR58) "Fear, Anxiety, Anxiety Disorders" funded by the German Research Foundation (DFG) and was registered beforehand at ClinicalTrials.gov (ID: NCT03208400).

Patients were recruited via local advertisements, flyers, posters, social media, university recruitment systems, specialized outpatient centers, and medical practices. Anyone interested was initially screened via telephone to check for existing exclusion criteria. Those matching inclusion criteria were invited to a personal appointment. After explaining the study protocol and informing on the data privacy act, all patients gave written informed consent. Following this, patients filled in the Spider Phobia Questionnaire (SPQ; Klorman, Weerts, Hastings, Melamed, & Lang, 1974) to assess severity of their fear of spiders (for further details see 2.3.1. "Primary outcome criterion"). If they scored below the defined cut-off, study participation terminated at this point.

We included patients with spider phobia (i.e. specific phobia of the animal subtype) assessed with the structured clinical interview (SCID) for DSM-IV (Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997), who were aged between 18 and 65 years, right-handed, fluent in German language, had a Caucasian descent (back to maternal and paternal grandparents; limited to Caucasian descent due to genetic analyses/genotyping), and were willing to participate in a highly controlled behavioral exposure delivered via VR. Exclusion criteria comprised a lifetime

diagnosis of other comorbid ADs like PD, PD/AG, SAD, GAD, OCD, PTSD, severe MDD, borderline personality disorder, bipolar I disorder, psychotic disorders, substance dependence (except nicotine) or acute suicidality. Comorbid mild to moderate depression (unless currently treated) and other SPs of the animal subtype were allowed if spider phobia was the primary diagnosis. Patients with current (psycho-)pharmacological treatment, current or past psychotherapy, neurological diseases, pregnant women, and those fulfilling MRI-related exclusion criteria were excluded. After study completion, patients received an expense allowance of €100. If patients dropped out at an earlier stage, they were partially compensated. In total, 100 patients were included, for further details see figure 8.

Sample characteristics were analyzed using χ^2 and *t*-tests. Effects of the VR exposure treatment were analyzed with two repeated-measures ANOVAs with the within-subject factor SPQ sum score (pre, post) and the within-subject factor BAT final distance (pre, post).

All statistical analyses were carried out using SPSS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.); $p < 0.05$ indicates statistical significance.

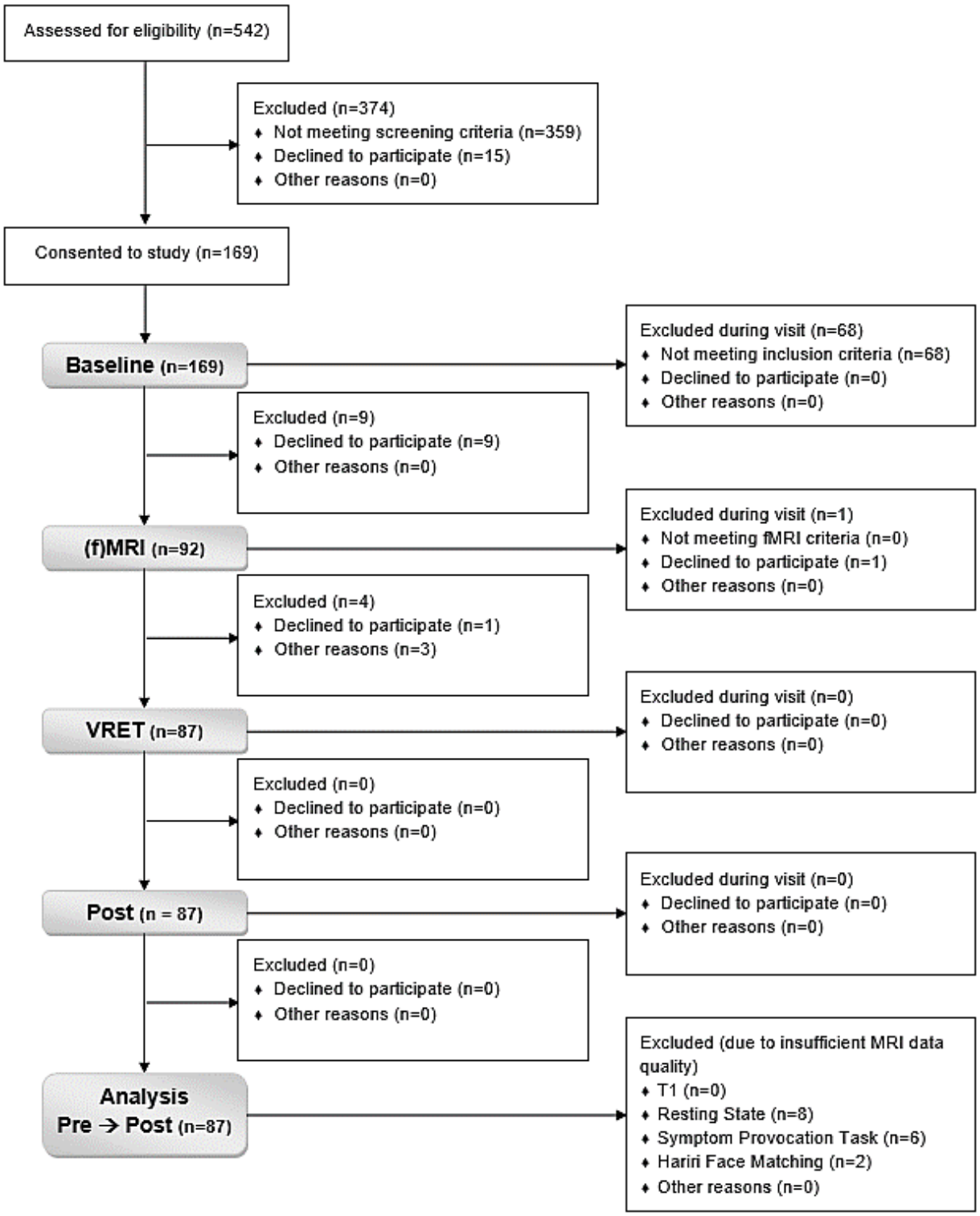

Figure 8. Flowchart. Overview of recruitment and inclusion numbers from pre- to post-treatment and number of datasets finally available for analyses. VRET: Virtual Reality Exposure Treatment.

2.2. Overview of study protocol

The study protocol has been reviewed by the Ethics Committee of the Medical Faculty at the University of Würzburg (proposal number 330/15), see figure 9 for a schematic representation. This clinical study was a bicentric (Würzburg and Münster) prospective-longitudinal investigation employing VR-exposure as a first-line treatment for SP. The intervention consisted of a massed one-session VR exposure treatment (VRET) . Since VRET is an effective treatment option compared to a waiting list (Garcia-Palacios, Hoffman, Carlin, Furness, & Botella, 2002) and comparable to evidence-based CBT (Opriş et al., 2012), no control condition was included. Instead, treatment responders and non-responders as indicated by pre-defined outcome measures (see below) were compared.

The study protocol started with the baseline assessment collecting clinical/psychometric, behavioral, and (epi-)genetic data; neuroimaging data were gathered in a separate MRI visit. Next, the intervention (VRET) took place. After the VRET, clinical/psychometric, behavioral, and (epi-)genetic data were assessed again in a post-treatment (mean time between VRET and post-assessment over both sites was 5.32 days with a standard deviation of 6.07 days) and in a 6-month follow-up (FU) assessment. Total duration including FU was approx. 30 weeks, the time between the first four visits was scheduled to be one week each.

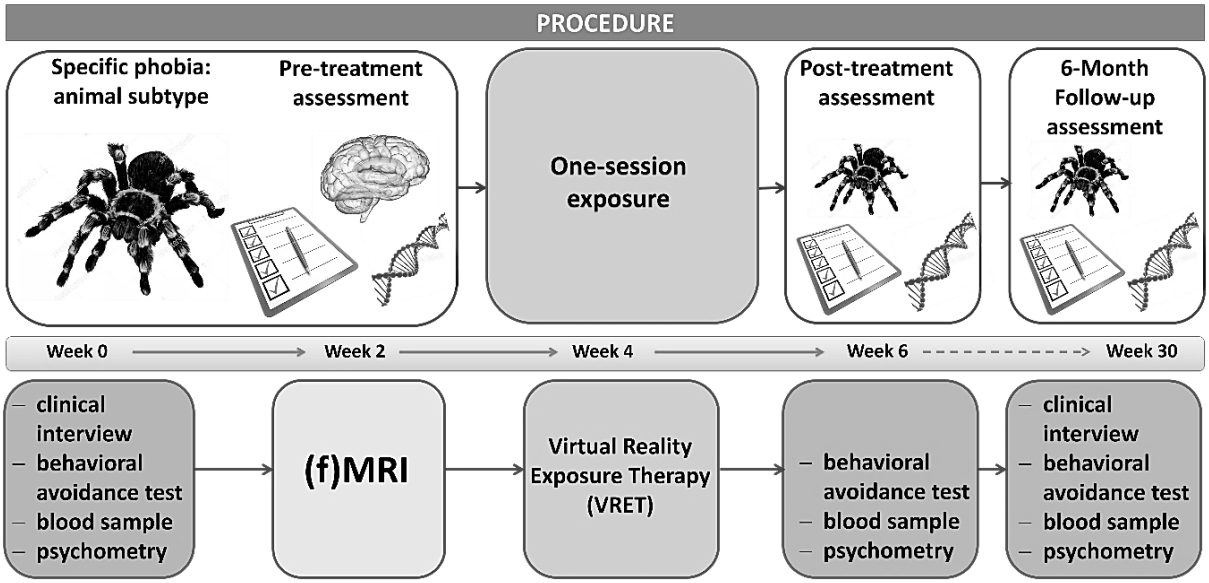

Figure 9. Schematic overview of the study protocol. Pre-treatment assessment encompasses a baseline assessment including, among others, clinical and psychometric data, and a behavioral avoidance test (BAT) serving as a quantification of avoidance behavior. A separate MRI session (structural and functional) completes the pre-treatment assessments. Treatment itself consists of a one-session massed exposure therapy in virtual reality. Approx. 1 week after treatment, clinical, behavioral data etc. are collected again. Baseline measurements will be repeated at the follow-up assessment 6 months after the post-treatment assessment.

Since for the present work and its hypotheses only clinical and (f)MRI assessments are relevant, all other aspects of the entire study protocol are not further outlined in detail. For additional information please see Schwarzmeier et al., 2020.

2.3. Assessments and outcomes

2.3.1. Primary outcome criterion: Spider Phobia Questionnaire

A German translation of the SPQ (Klorman et al., 1974) was used as a dimensional measure of psychopathology as this questionnaire is recommended to assess spider phobia (Hamm, 2006). The questionnaire consists of 31 items which have to be rated as 'true' or 'false', maximum score per item is 1. The English version shows a satisfactory internal consistency of 0.91 (Cronbach´s Alpha) and a test-retest correlation of 0.94 (Muris & Merckelbach, 1996).

A sum score of at least 20 was chosen as inclusion criterion, as this is the cut-off score for clinically significant symptom severity (Öst, 1996). A reduction of at least 30% of the SPQ sum score from pre- to post-assessment was selected to characterize clinically meaningful treatment response. SPQ scores were assessed pre-treatment, post, and after 6-month FU.

2.3.2. Secondary outcome criterion: Behavioral Avoidance Test

An in vivo behavioral avoidance test (BAT; see figure 10) was used to assess generalization of treatment effects to a real living spider. A bird spider (Grammostola rosea) was placed in a plastic box with a closed lid. The box was placed on a slide 3m away from the patient who was then asked to slowly drag the box with the spider towards him-/herself as close as possible by using a crank. The final distance between patient and spider (in cm, quantification of avoidance behavior) served as the dependent variable.

During the BAT, electrodermal activity (EDA) was recorded alongside with Ag/AgCl electrodes on the hypothenar of the left hand using isotonic electrode paste as contact medium and Brain Vision hard- and software for data acquisition (Brain Vision ExG Amplifier and Brain Vision Recorder; Brain Products, Munich, Germany).

Patients were also asked to rate their fear on a scale from '0 = no fear at all' to '100 = extremely strong fear' for given anchor points (anticipation, at the doorstep, beginning of the BAT, after final distance, end of the BAT, after spider left the room). In addition, observation of concomitant behavior was noted using a standardized scheme (i.e., if the patient can tolerate the stepwise approaching spider).

All BAT outcomes were assessed pre-treatment, post, and after 6-month FU. A reduction of at least 50% of the final distance from pre- to post-assessment characterized the secondary outcome of treatment response.

Figure 10. In vivo BAT. A bird spider is placed in a plastic box with a closed lid. The box is placed on a slide 3 m away from the patient who then slowly drags the box with the spider towards himself as close as possible using a crank. The final distance between patient and spider (i.e. quantification of avoidance behavior) serves as the dependent variable. Patients are asked to rate their fear, observation of behavior is noted using a standardized scheme and electrodermal activity (EDA) is recorded alongside. All outcomes are assessed pre-treatment, post, and after 6-month follow-up. BAT: Behavioral Avoidance Test.

2.3.3. Additional clinical and psychometric assessments

The SCID for DSM-IV-TR Axis I Disorders (American Psychiatric Association, 2000) was conducted to confirm the diagnosis of primary spider phobia and to check for comorbid diagnoses pre-treatment and at FU.

Moreover, the Clinical Global Impressions Scale (CGI-S; Guy, 1976) was used to rate symptom severity pre-treatment, post, and at FU. Several questionnaires were assessed via the online-survey application LimeSurvey (LimeSurvey GmbH, Hamburg, Germany) at all three

assessment dates. An overview of all questionnaires and assessments can be found in the appendix (table S1).

A paper-and-pencil interview to assess avoidance behavior, encounters with spiders (actively precipitated or accidentally), experienced fear compared to pre-treatment, and an evaluation of the VRET intervention was also handed out at FU.

2.4. Imaging battery

2.4.1. (f)MRI assessments

First, an anatomical T1-weighted image was obtained, followed by a resting state measurement (8min) to assess the functional organization of the brain at rest without any specific task-related activation.

The first task was the Sustained and Phasic Fear Paradigm (SPF; Münsterkötter et al., 2015) investigating the neural networks involved in the processing of a phasic fear response towards an actual threat and in the processing of anticipatory sustained anxiety towards an imminent and unpredictable hazard. It consisted of 15 active and 14 inactive runs (block design). During inactive blocks, participants fixated on a dot presented in the middle of the screen for 15s. Active blocks consisted of 10 pictures each presented for 1.7s and followed by a fixation dot (300ms). Three fear conditions were presented in pseudorandomized order: in the sustained fear condition, where participants were told that pictures of spiders could appear, pictures of empty rooms were presented and in one-third of the runs, a picture of a spider appeared in the last quarter of the run. In the phasic fear condition, participants were instructed that they will see pictures of spiders, whereas in the no fear (i.e. safety) condition only pictures of empty rooms were presented. Each fear condition was presented five times followed by a no-stimulus block, respectively. After each active run, participants evaluated their subjective appraisal regarding the pictures on a 4-point scale (‘1 = very pleasant’, ‘2 = pleasant’, ‘3 = unpleasant’, ‘4 = very unpleasant’). Total task duration was 9:45min.

In addition, the Hariri face-matching paradigm, which is widely used to investigate amygdala responsiveness to fearful and angry faces (e.g. Dannlowski et al., 2011; Hariri et al., 2002) was conducted. Since this paradigm is not relevant to the present study, no further details are reported here.

2.4.2. (f)MRI data acquisition and quality control pathway

A 3-Tesla MRI scanner (Siemens Skyra) was used. The structural T1-weighted data set was collected using magnetization prepared rapid gradient echo (MPRAGE: matrix = 256 x 256,

slices = 176, FOV = 256, voxel size = 1x1x1mm, TE = 2.26ms, TR = 1.9s, flip angle = 9°). Functional images were collected with a T2*-weighted EPI sequence sensitive to BOLD contrast in ascending order (matrix = 64 x 64, slices = 33, FOV = 210, voxel size = 3.3x3.3x3.8 mm, slice thickness = 3.8mm, 10% slice gap, TE = 30ms, TR = 2.0s, flip angle = 90°). Slices covered the whole brain and were positioned transaxially parallel to the AC-PC line with a tilted angle of 20°. Stimuli were presented via MR-compatible LCD goggles and headphones (VisuaStim Digital Goggles & Headphones, Resonance Technology Inc., Northridge, CA, USA) using Presentation 14 (Neurobehavioral Systems; www.neurobs.de).

MRI data quality control encompassed visual inspection of the structural T1 image concerning anatomy and artifacts (e.g. motion artifacts, ghosting etc.). fMRI data quality control encompassed visual inspection of functional activation patterns for the first-level contrasts as well as close scrutiny of movement and rotation parameters. A global value (min-max range) for movement (x/y/z axis) or rotation (pitch/roll/yaw) greater than 3.3mm or resp. 3.3° led to preclusion. Peak values (max. value from one scan to another) greater than 3.3mm or resp. 3.3° were also discarded. Global and peak values were checked for each subject. Exclusions due to poor quality control parameters are listed in the flowchart (figure 8).

2.4.3. Neuroimaging analysis pathway

For all analyses, independent of modality, subjects were grouped together according to the primary outcome criterion (SPQ), the secondary outcome criterion (BAT), and the within-session (ws) extinction, i.e. the mean magnitude of fear reduction throughout the behavioral exposure session. All subjects showing a reduction of at least 30% or more in the SPQ sum score were classified as SPQ-responders. All subjects showing a reduction of at least 50% or more in the final distance in the BAT were classified as BAT-responders. The classification into high and low ws extinction was performed by using a median split to keep the binarity analogously to the primary and secondary outcome classification schema, which means any value below the median is categorized as low ws extinction, and every value above as high ws extinction. These three resulting groups were each tested as separate entities.

Since group and site (Würzburg and Münster) comparisons revealed significant differences concerning the variables age, the SPQ sum score at baseline, and the duration of the exposure session, these were entered as second-level covariates of no interest in all following analyses, as independent replication between sites is planned. Although the CGI score and the age of onset differed significantly between groups, they were not included as covariates. Firstly, to avoid overfitting and secondly, due to the following considerations: The age of onset is a

problematic measure, since it is assessed retrospectively, and most patients cannot precisely recall an onset timepoint. Furthermore, it correlates with age. The CGI is a measure of symptom severity, like the SPQ. However, the SPQ represents the better statistical choice since it is an interval-scaled variable.

Task-based functional activation and behavioral data: SPF

Functional images were spatially and temporally aligned, unwarped (i.e., movement-by-susceptibility-induced variance in fMRI time series is estimated and removed), normalized into standard stereotactic space, and smoothed with a 6-mm FWHM Gaussian kernel. The BOLD response for each condition of the SPF paradigm (phasic fear, sustained fear, no fear, baseline = inactive blocks with fixation dots) was modeled by the canonical hemodynamic response function (HRF) using the GLM to analyze brain activation differences related to the onset of the different stimuli. Instructions and ratings were included in the model as regressors of no interest.

Parameter estimates (β), *t*- and *F*-statistic images were calculated. First-level *t*-contrasts were calculated for phasic fear > sustained fear, sustained fear > phasic fear, phasic fear > no fear, sustained fear > no fear, phasic fear > baseline, and sustained fear > baseline. Additionally, the effect of interest (EoI) was assessed with a first-level omnibus *F*-test. After quality control, a total of N = 81 datasets was available. Functional data analyses were carried out using Statistical Parametric Mapping 8 (SPM8; www.fil.ion.ucl.ac.uk/spm/software/spm8/) implemented in MATLAB® R2012b (Mathworks Inc., USA).

The main task effect for the contrast of interest, phasic fear > no fear, was analyzed with a one-sample *t*-test for the whole sample within small volume corrections (SVCs; FWE-corrected at $p < 0.05$ with a cluster-forming threshold at $p < 0.001$) in the following pre-defined fronto-limbic regions of interest (ROIs) using unilateral (left/right) AAL (Tzourio-Mazoyer et al., 2002) masks generated with the WFU pick atlas toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003): amygdala, insula, ACC, hippocampus, thalamus, SMA, superior frontal gyrus (dorsolateral, orbital, medial part), middle frontal gyrus (middle, orbital, medial orbital part), inferior frontal gyrus (pars triangularis, pars opercularis, pars orbitalis), and the gyrus rectus. In addition, an exploratory whole-brain analysis was carried out ($p < 0.05$, FWE-corrected, cluster-extent threshold $k_E = 10$).

Two-sample *t*-test group comparisons were conducted using the first-level phasic fear > no fear contrast images. Groups were defined as follows: **1)** SPQ: group 1 (n = 52): responders, group 2 (n = 29): non-responders **2)** BAT: group 1 (n = 42): responders, group 2 (n = 39): non-responders **3)** ws extinction: group 1 (n = 40): high, group 2 (n = 41): low. SVCs (FWE-

corrected at $p < 0.05$ with a cluster-forming threshold at $p < 0.001$) using the same ROIs as outlined above were computed. Exploratory whole-brain analyses ($p < 0.001$, $k_E = 10$) were performed afterwards. Beta values from significantly activated brain clusters were extracted using a 5mm sphere and used for bar graph visualization.

Subjective ratings of the SPF conditions were analyzed for the whole sample with a repeated-measures ANOVA with the within-subject factor condition (phasic fear, sustained fear, no fear) followed by pairwise comparisons to localize the direction of effects. To ensure that there are no systematic rating differences within the different groups, repeated-measures ANOVA with the according group factor were calculated to examine the interaction between conditions and groups separately. Where sphericity assumptions were not met according to the Mauchly-Test, Greenhouse-Geisser corrections were applied; where normal distribution assumptions were not met, non-parametric equivalent procedures were applied; $p < 0.05$ indicates statistical significance. Statistical analyses were carried out using SPSS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Due to missing data, a total of N = 80 datasets was available.

Psychophysiological interaction (PPI): Task-based functional connectivity

Functional connectivity is based on statistical dependencies between two sets of neurophysiological data, i.e. the temporal correlation between the time series of two brain regions. In fMRI, these time series are available for each voxel of the brain. Functional connectivity maps can be computed for specific seed regions to identify sets of voxels whose time series demonstrate distinct components of the covariance structure of the data (Stephan & Friston, 2009).

A psychophysiological interaction (PPI) states that the contribution of one brain region to another changes significantly with the experimental or psychological context (Friston et al., 1997). Time series data can not only inform about task-related activity, but also about the functional connectivity between specific regions and the influence of behavioral or physiologic states on that connectivity (Gitelman, Penny, Ashburner, & Friston, 2003).

The idea is, that covariance between brain regions changes dependent on the specific task and its content. The difference in regional covariance due to the task is tested by analyzing differences in regression slopes. The PPI model integrates a psychological variable (i.e. the task, condition etc.), a physiological variable (i.e. the time series of a specific seed region in the brain), and the interaction term between these both variables. This term is created by multiplication of the deconvolved seed region time series by the condition vector. However, PPI does not allow drawing inference on the direction of influence (Britton et al., 2009).

In this analysis, the selected seed ROI was within the left amygdala and was chosen from our preceding fMRI analyses, where it yielded a significant effect. The coordinates for the volume of interest (VOI) extraction were taken from the results of the main task effect of the whole sample for the contrast phasic fear > no fear [MNI coordinates (-24, -4, -18)]. The principal eigenvariate was extracted within a sphere of 5 mm radius around the VOI.

A model incorporating the psychological variable, the time course of the left amygdala, and the interaction term was built for every single subject to explore task-dependent connectivity patterns, i.e. to examine whether the covariance between regions varied by task (phasic fear > no fear). Individual voxel-wise contrast images were generated.

On the combined group level, the resulting contrast image for each subject was entered in a one-sample *t*-test to assess main connectivity by identifying regions showing changes in connectivity with the seed region depending on the experimental context (phasic fear > no fear) within the whole sample. This PPI reveals regions which were more synchronously activated in response to the phasic fear condition than in response to the no fear condition.

Furthermore, differences in task-based connectivity between the groups were assessed using two-sample *t*-tests. Groups were defined as follows: **1)** SPQ: group 1 (n = 52): responders, group 2 (n = 29): non-responders **2)** BAT: group 1 (n = 42): responders, group 2 (n = 39): non-responders **3)** ws extinction: group 1 (n = 40): high, group 2 (n = 41): low. SVCs (FWE-corrected at $p < 0.05$ with a cluster-forming threshold at $p < 0.001$) using the same ROIs as outlined above were computed. Exploratory whole-brain analyses ($p < 0.05$, FWE-corrected, $k_E = 10$ for main connectivity; $p < 0.001$, $k_E = 10$ for group comparisons) were performed afterwards. These PPIs reveal regions which were more synchronously activated in response to the phasic fear condition than in response to the no fear condition between the different groups.

All analyses were carried out using the PPI module implemented in Statistical Parametric Mapping 8 (SPM8; www.fil.ion.ucl.ac.uk/spm/software/spm8/) implemented in MATLAB® R2012b (Mathworks Inc., USA).

Brain morphometry

After quality control, a total of N = 87 datasets was available, since no structural datasets had to be excluded. Preprocessing steps included the normalization of all T1 images to a template space and the segmentation into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF). After preprocessing, the normalized and segmented data were quality checked and sample homogeneity was scrutinized. GM images were then smoothed with an 8-mm FWHM Gaussian kernel before entering them into a statistical model.

Throughout preprocessing, the total intracranial volume (TIV) was estimated for every subject. TIV is strongly recommended to be included as a covariate for all voxel-based morphometry analyses to correct for different brain sizes. However, TIV should not highly correlate with the entered parameters of interest; otherwise, parts of the variance explained by the parameters of interest will be removed alongside with TIV. This correlation was assessed beforehand by checking for design orthogonality (for further details see www.neuro.uni-jena.de/cat12/CAT12-Manual.pdf).

Analyses were carried out using the Computational Anatomy Toolbox (CAT12; version CAT12.6 (r1450) from 2019-04-04; www.neuro.uni-jena.de/cat/) for Statistical Parametric Mapping 12 (SPM12; www.fil.ion.ucl.ac.uk/spm/software/spm12/) implemented in MATLAB® R2012b (Mathworks Inc., USA). Since some steps (e.g. smoothing) are not implemented in the CAT12 toolbox, they were carried out using SPM12. In addition to the main covariates TIV and gender (due to sex differences in human brain structure, for a meta-analysis, see for example Ruigrok et al., 2014) were also entered as covariates of no interest. All other parameters remained the recommended default settings.

For group comparisons, two-sample *t*-tests were conducted on grey matter volume (GMV). Groups were defined as follows: **1)** SPQ: group 1 (n = 56): responders, group 2 (n = 31): non-responders **2)** BAT: group 1 (n = 45): responders, group 2 (n = 42): non-responders **3)** ws extinction: group 1 (n = 44): high, group 2 (n = 43): low. For the ws extinction group, which is categorized via median split, 4 subjects´ value was the median itself, therefore they were equally divided at random into the high and the low group. SVCs (FWE-corrected at $p < 0.05$ with a cluster-forming threshold of $p < 0.001$) were computed using the same ROIs as before.

ROI-analyses were followed by exploratory whole-brain analyses with a significance level at $p < 0.001$, cluster-extent thresholds were determined empirically for each *t*-test accordingly to the CAT12 manual (SPQ & BAT: $k_E = 86$, ws extinction: $k_E = 85$). All brain regions were labeled according to the AAL in DARTEL space implemented within CAT12.

2.5. Virtual Reality Exposure Therapy (VRET)

VRET was manualized and study therapists were trained in cooperation. In preparation for the VRET, patients were given a detailed psychoeducational manual (adapted from Herrmann et al., 2017) to read at home outlining the function of fear, its components, and their interplay in general (vicious circle of fear), and more specific transferred to spider phobia and how it should be treated. Its content was discussed and explained before the VRET session started to clarify the rationale of behavioral exposure and its mechanism of action, which is suggested to induce

new, inhibitory fear learning (Craske, Liao, Brown, & Vervliet, 2012). Patients also had the opportunity to ask questions.

Before and after the VRET, patients completed a protocol assessing their expectations and apprehensions and which of them eventuated. The Igroup Presence Questionnaire (IPQ; Schubert, 2003) was used for measuring the sense of presence experienced in a virtual environment. The software used (VT+ research systems, VTplus GmbH, Würzburg) provides several scenarios from which five standard scenarios every patient should ideally complete were selected. The spiders used in the chosen VRET-scenarios differed. However, they were not exactly the same as the Grammostola rosea bird spider used in the in vivo BAT. While in the first scenario the spider is quite small and black, the spiders in the other scenarios rather resemble a cross spider, although with an unrealistic body size. To achieve context generalization, the size of the spider, the number of spiders, and the situational conditions were manipulated.

Before (anticipatory anxiety) and throughout the scenarios, patients were constantly asked to give fear ratings on a scale from '0 = no fear at all' to '100 = extremely strong fear'. Within each scenario, we defined specific anchor points (e.g. standing right below the spider hanging from the doorframe etc.) that should be achieved by each patient. If the fear rating was < 20 or if the rating was stagnating three times in succession, patients proceeded with the next scenario. The number of fear ratings and the time interval between them were adapted on an individual level.

The VR environment was generated using Steam Source engine (Valve Corp., Bellevue, Washington, USA) and displayed via a Z800 3D Visor head-mounted display (HMD; eMagin, NY, USA). Maximum duration of the intervention was 2.5 hours.

Description of VR scenarios

1) After an accommodation phase to the VR environment, the first scenario started with a rather small but moving spider placed in a plastic box without a lid. Patients had to approach the box as close as possible and bend over it to watch the spider carefully.
2) The second scenario consisted of a bigger spider hanging from the doorframe and patients had to walk towards that door and finally stop in the doorframe beneath the spider and look up to it.
3) In the third scenario, a big spider was crawling on the floor and patients had to approach, to obstruct the way, and to crouch down.
4) The fourth scenario contained two spiders, one on the floor and one on the wall. Patients had to approach, to focus only on the spider on the floor, and to crouch down.

5) In the fifth and last scenario, four big spiders were crawling on the floor. Patients had to approach two of them and to crouch down.

3. Results

3.1. Sample characteristics

The proportional overlap between the three different group classifications is demonstrated in table 4.

Table 4. Overlap between the different group classifications.

	overlap
SPF sample	
SPQ responders & BAT responders	61.54 %
SPQ responders & high ws extinction	57.69 %
BAT responders & high ws extinction	50.00 %
Morphometry sample	
SPQ responders & BAT responders	62.50 %
SPQ responders & high ws extinction	58.93 %
BAT responders & high ws extinction	53.33 %

SPF: Sustained and Phasic Fear paradigm; SPQ: Spider Phobia Questionnaire; BAT: Behavioral Avoidance Test; ws extinction: within-session extinction.

Sample characteristics for the whole sample and grouped by the primary outcome criterion for the SPF (N = 81) and the morphometry sample (N = 87) are given in table 5 and table 6. Sample characteristics for both samples grouped by the secondary outcome criterion and the ws extinction can be found in the appendix (see tables S2 – S5).

Table 5. Sample characteristics for the whole SPF-sample and grouped by the primary outcome criterion SPQ (N = 81).

	all n =81 (100%)	responders n = 52 (64.20%)	non-responders n = 29 (35.80%)	χ^2 or *t* (df)	*p*
Demographic characteristics					
Age (years)	28.64 (88.86)	26.67 (7.21)	32.17 (10.46)	2.79 (79)	<0.05
Female gender [n (%)]	70 (86.42)	44 (84.62)	26 (89.66)	0.40 (1)	0.526
Years of education	14.42 (3.30)	14.46 (3.36)	14.34 (3.27)	-0.15 (79)	0.880
Clinical and psychometric characteristics					
SPQ sum score	23.12 (2.43)	23.65 (2.42)	22.17 (2.17)	-2.73 (79)	<0.05
BAT final distance (cm)	169.10 (61.69)	179.77 (60.95)	149.97 (59.30)	-2.13 (79)	<0.05
Duration exposure session (min)	85.88 (25.88)	83.79 (25.13)	89.62 (27.21)	0.97 (79)	0.334
Within-session extinction	45.64 (19.08)	48.98 (18.65)	39.65 (18.68)	2.16 (79)	<0.05
Age of onset	8.03 (3.89)[a]	8.43 (4.16)[b]	7.29 (3.29)[c]	-1.26 (77)	0.213
Comorbidity [n (%)]	2(2.47)	1 (1.92)	1 (3.45)	0.18 (1)	0.672
major depression	2 (2.47)	1 (1.92)	1 (3.45)		
subordinate animal phobia	0 (0.00)	0 (0.00)	0 (0.00)		
CGI [n (%)]				13.18 (3)	<0.05
Mildly ill	15 (18.52)	4 (7.69)	11 (37.93)		
Moderately ill	31 (38.37)	20 (38.46)	11 (37.93)		
Markedly ill	34 (41.98)	27 (51.92)	7 (24.14)		
Severely ill	1 (1.23)	1 (1.92)	0 (0.00)		
FEAS anxiety	101.54 (14.14)[d]	103.52 (14.74)	97.86 (12.36)[e]	-1.73 (78)	0.088
FEAS disgust	110.06 (12.11)[f]	111.27 (12.95)	107.82 (10.20)[g]	-1.22 (78)	0.227
STAI- Trait	36.21 (9.20)	36.23 (9.24)	36.17 (9.29)	-0.03 (79)	0.978
BDI-II total	3.30 (4.24)	3.23 (4.14)	3.41 (4.48)	0.19 (79)	0.854
ASI-3	15.16 (9.98)	14.42 (8.70)	16.48(11.99)	0.81 (44.72)	0.420
GSE	2.94 (0.43)	3.01 (0.38)	2.82 (0.50)	-1.90 (79)	0.061

SPQ: Spider Phobia Questionnaire; BAT: Behavioral Avoidance Test; CGI: Clinical Global Impression; FEAS: Fragebogen zu Ekel und Angst vor Spinnen (questionnaire regarding disgust and fear of spiders) , STAI: State Trait Anxiety Inventory; BDI-II: Beck Depression Inventory II, ASI-3: Anxiety Sensitivity Index; GSE: General Self Efficacy Scale.

[a] available for n = 79; [b] available for n = 51; [c] available for n = 28; [d] available for n = 80; [e] available for n = 28; [f] available for n = 80; [g] available for n = 28. Values given as mean (standard deviation) except where noted.

Table 6. Sample characteristics for the whole morphometry sample and grouped by the primary outcome criterion SPQ (N = 87).

	all N = 87 (100%)	responders n = 56 (64.37%)	non-responders n = 31 (35.63%)	χ^2 or *t* (df)	*p*
Demographic characteristics					
Age (years)	29.39 (9.63)	27.57 (7.94)	32.68 (11.52)	2.44 (85)	<0.05
Female gender [n (%)]	75 (86.21)	47 (83.93)	28 (90.32)	0.69 (1)	0.408
Years of education	14.33 (3.34)	14.23 (3.42)	14.52 (3.23)	0.38 (85)	0.706
Clinical and psychometric characteristics at baseline					
SPQ sum score	23.09 (2.36)	23.61 (2.35)	22.16 (2.01)	-2.85 (85)	<0.05
BAT final distance (cm)	171.96 (62.26)	181.22 (61.60)	155.23 (60.88)	-1.89 (85)	0.062
Duration exposure session (min)	86.51 (25.83)	84.59 (25.43)	89.97 (26.60)	0.93 (85)	0.355
Within-session extinction	45.99 (19.34)	49.61 (18.96)	39.45 (18.56)	2.41 (85)	<0.05
Age of onset	8.22 (4.05)[a]	8.84 (4.34)[b]	7.10 (3.25)[c]	-2.08 (74.77)	<0.05
Comorbidity [n (%)]	3 (3.45)	1 (1.79)	2 (6.45)	2.03 (2)	0.362
major depression	2 (2.30)	1(1.79)	1 (3.23)		
subordinate animal phobia	1 (1.15)	0 (0.00)	1 (3.23)		
CGI [n (%)]				12.49 (3)	<0.05
Mildly ill	15 (17.24)	4 (7.14)	11 (35.8)		
Moderately ill	32 (36.78)	21 (37.50)	11 (35.8)		
Markedly ill	37 (42.53)	29 (51.79)	8 (25.81)		
Severely ill	3 (3.45)	2 (3.57)	1 (3.23)		
FEAS anxiety	101.59 (14.14)[d]	103.32 (14.57)	98.67 (12.93)[e]	-1.56 (84)	0.122
FEAS disgust	110.26 (11.94)[f]	111.30 (12.72)	108.30 (10.23)[g]	-1.11 (84)	0.269
STAI- Trait	36.29 (9.00)	36.34 (9.05)	36.19 (9.05)	-0.72 (85)	0.943
BDI-II total	3.52 (4.24)	3.46 (4.17)	3.61 (4.42)	0.16 (85)	0.877
ASI-3	15.56 (9.95)	14.61 (8.57)	17.29 (12.00)	1.10 (47.28)	0.277
GSE	2.94 (0.42)	3.00 (0.36)	2.83 (0.49)	-1.78 (85)	0.078

SPQ: Spider Phobia Questionnaire; BAT: Behavioral Avoidance Test; CGI: Clinical Global Impression; FEAS: Fragebogen zu Ekel und Angst vor Spinnen (questionnaire regarding disgust and fear of spiders), STAI: State Trait Anxiety Inventory; BDI-II: Beck Depression Inventory II, ASI-3: Anxiety Sensitivity Index; GSE: General Self Efficacy Scale.

[a] available for n = 85; [b] available for n = 55; [c] available for n = 30; [d] available for n = 86; [e] available for n = 30; [f] available for n = 86; [g] available for n = 30. Values given as mean (standard deviation) except where noted.

The effects of the VRET (for the morphometry sample, N = 87) are depicted in figure 11. The SPQ sum score was significantly lower (F (1, 86) = 300.34, $p < 0.001$) at post- (M = 15.17) than at pre-treatment (M = 23.09). The final distance in the BAT was also significantly reduced (F (1, 86) = 185.19, $p < 0.001$) from pre- (M = 171.96) to post-treatment (M = 77.98).

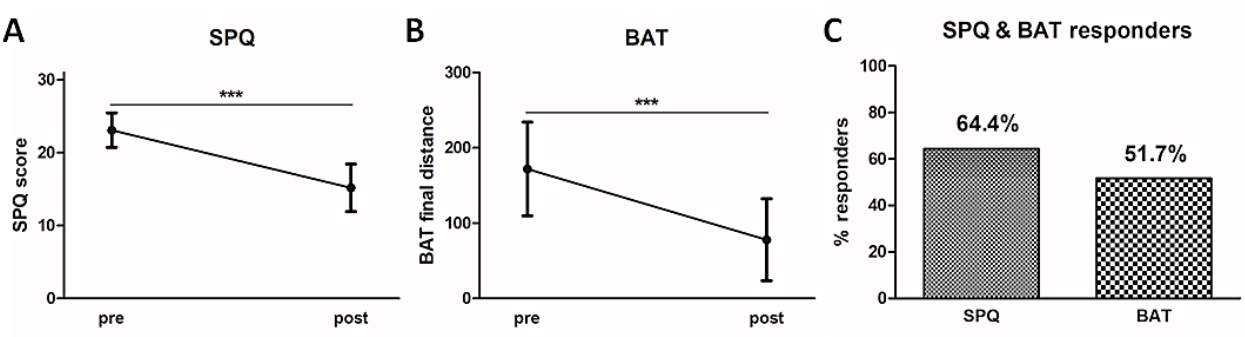

Figure 11. Effects of the VRET from pre (baseline) to post. A. SPQ sum score. Maximum score = 31. **B.** Final distance in the BAT in cm. Maximum distance = 300cm. **C.** Percentage of responders according to pre-defined primary (SPQ) and secondary (BAT) outcome criteria. SPQ: Spider Phobia Questionnaire; BAT: Behavioral Avoidance Test. ***$p < 0.001$.

3.2. SPF-paradigm

If not explicitly indicated for fMRI data, results from ROI analyses are reported.

3.2.1. Behavioral data

A whole sample repeated-measures ANOVA for the subjective ratings throughout the SPF-task (figure 12) demonstrated a significant difference between the three conditions (F (1.82, 143.36) = 515.74, $p < 0.001$). Pairwise comparisons (non-parametric Wilcoxon signed-rank tests since rating data from two conditions were not normally distributed) revealed that the phasic fear condition (Mdn = 4) was rated significantly more unpleasant than the sustained fear condition (Mdn = 2.33), z = -7.57, $p < 0.001$ and the no fear condition (Mdn = 1.2), z = -7.69, $p < 0.001$. The sustained fear condition was also rated significantly more unpleasant than the no fear condition, z = -7.48, $p < 0.001$.

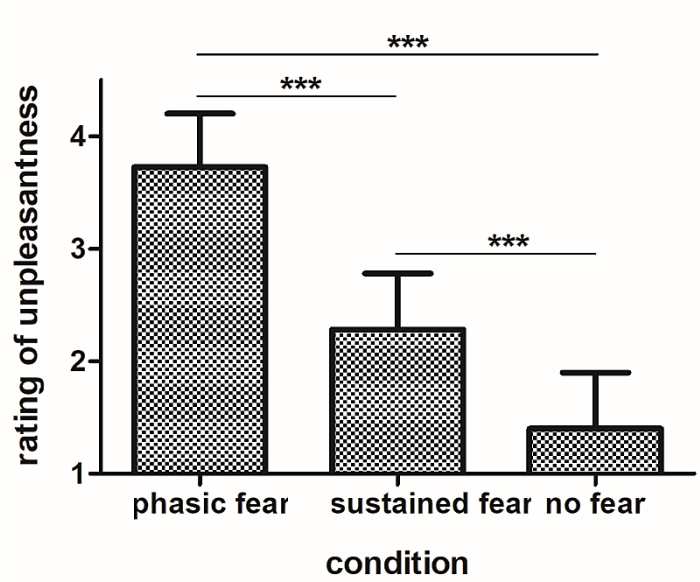

Figure 12. Behavioral rating data of the SPF paradigm for the whole sample. Ratings of pleasantness were collected for all three conditions. 1 = very pleasant, 2 = pleasant, 3 = unpleasant, 4 = very unpleasant. Means with standard deviation (SD) are displayed. SPF: Sustained and Phasic Fear paradigm. *** $p < 0.001$.

To ensure that there are no systematical rating differences within the different groups, the group factor was included in three separate analyses which yielded comparable results for all groups. Results can be found in the appendix (see figures S1 – S3).

3.2.2. Main task effects

In response to the contrast phasic fear > no fear the combined sample exhibited activation in, among others, the bilateral hippocampus, bilateral thalamus, bilateral insula, bilateral

amygdala, bilateral ACC, bilateral SMA, bilateral IFO, bilateral SFG, bilateral IFG, and bilateral MFG (see table 7 and figure 13).

Whole-brain analyses additionally revealed, inter alia, activation in the left IOG and MOG, the precentral gyrus, and the cerebellum (see table S6 in the appendix).

Table 7. Brain activation in ROIs for the contrast phasic fear > no fear and main connectivity of the seed region based on the contrast phasic fear > no fear for the combined sample.

Contrast/region	side	voxels	x	y	z	*t*	*p*
Main task effects							
SPF: phasic fear > no fear							
Hippocampus	L	396	-20	-30	4	16.79	<0.001
Hippocampus	R	424	20	-28	-6	15.48	<0.001
Thalamus	L	678	-20	-28	-2	15.37	<0.001
Thalamus	R	651	20	-28	-2	13.92	<0.001
Insula	R	803	38	12	-6	8.30	<0.001
Amygdala	L	40	-24	-4	18	7.90	<0.001
Anterior cingulate cortex	R	151	2	18	26	7.74	<0.001
Supplementary motor area	R	513	10	2	74	7.44	<0.001
Amygdala	R	78	32	-2	-14	7.42	<0.001
Anterior cingulate cortex	L	174	-2	18	26	7.26	<0.001
Insula	L	798	-36	8	-2	6.83	<0.001
Middle frontal gyrus	R	61	52	0	52	6.55	<0.001
Supplementary motor area	L	145	-6	4	74	5.54	<0.001
Inferior frontal gyrus, pars orbitalis	R	62	46	18	-12	5.49	<0.001
Inferior frontal operculum	L	60	-40	4	22	5.29	<0.001
Inferior frontal operculum	R	45	48	10	0	5.24	<0.001
Inferior frontal gyrus, pars triangularis	R	9	36	28	2	5.22	0.001
Superior frontal gyrus	L	24	-22	48	40	5.08	0.002
Superior frontal gyrus	R	60	14	2	72	4.86	0.004
Middle frontal gyrus	L	28	-24	50	36	4.75	0.006
Inferior frontal gyrus, pars orbitalis	L	21	-38	16	-16	4.60	<0.001
Superior frontal gyrus	L	53	-12	2	72	4.41	0.015
Superior frontal gyrus, orbital part	L	1	-26	14	-14	4.41	<0.001
Inferior frontal gyrus, pars orbitalis	L	1	-34	18	-14	4.29	0.001
Inferior frontal operculum	R	53	42	6	24	4.11	0.015
Inferior frontal gyrus, pars triangularis	R	22	46	34	6	3.96	0.032
Medial superior frontal gyrus	L	5	-60	60	34	3.91	0.041
Inferior frontal operculum	L	3	-38	6	10	3.72	<0.001
Inferior frontal gyrus, pars orbitalis	R	1	34	14	-20	3.70	0.025
Main connectivity							
PPI: seed region left amygdala* and phasic fear > no fear							
Hippocampus	R	193	28	-26	-8	5.75	<0.001
Hippocampus	L	117	-20	-30	-4	5.06	<0.001
Thalamus	L	13	-20	-28	-2	4.78	0.001
Thalamus	R	13	16	-30	-2	4.56	0.002

*5mm-sphere around MNI coordinates (-24, -4,-18) from main task effects
L: left; R: right; voxel: number of voxels per cluster; x, y, z: MNI coordinates; SPF: Sustained and phasic fear paradigm; PPI: psychophysiological interaction. ROI peak voxels are given. Small volume corrections in pre-defined ROIs (FWE-corrected at $p < 0.05$) with a cluster-forming threshold of $p < 0.001$.

3.2.3. Group comparisons

All ROI group comparisons can be found in table 8 and figure 14, whole-brain results in table S7 in the appendix.

Primary outcome criterion (SPQ)

There were no significant differences between responders and non-responders in ROIs.

Whole-brain analyses showed a stronger activation in the left lingual gyrus in response to the contrast phasic fear > no fear in responders compared to non-responders. No significant differences were found for the reverse contrast.

Secondary outcome criterion (BAT)

BAT non-responders exhibited stronger activation in the bilateral medial SFG, left SMA, and right IFO. No significant differences were found for the reverse contrast for responders > non-responders.

In the whole-brain analyses, among others, the left superior parietal lobule, the right inferior temporal gyrus (ITG), the right mid- and posterior cingulate cortex, and the left MFG were stronger activated in non-responders than responders, while there were no significant differences for the reverse contrast responders > non-responders.

Within-session extinction

Patients within the low extinction group showed heightened activation in, among others, the right IFO, right IFG, and left SMA compared to the high extinction group. No significant differences were found for the reverse contrast.

Whole-brain analyses additionally showed heightened activation in, inter alia, the left inferior parietal lobule, left precuneus, right supramarginal gyrus, left MFG, right SFG, right MOG, and right MTG in comparison to patients within the high extinction group. Contrasting the high > low group yielded no significant differences.

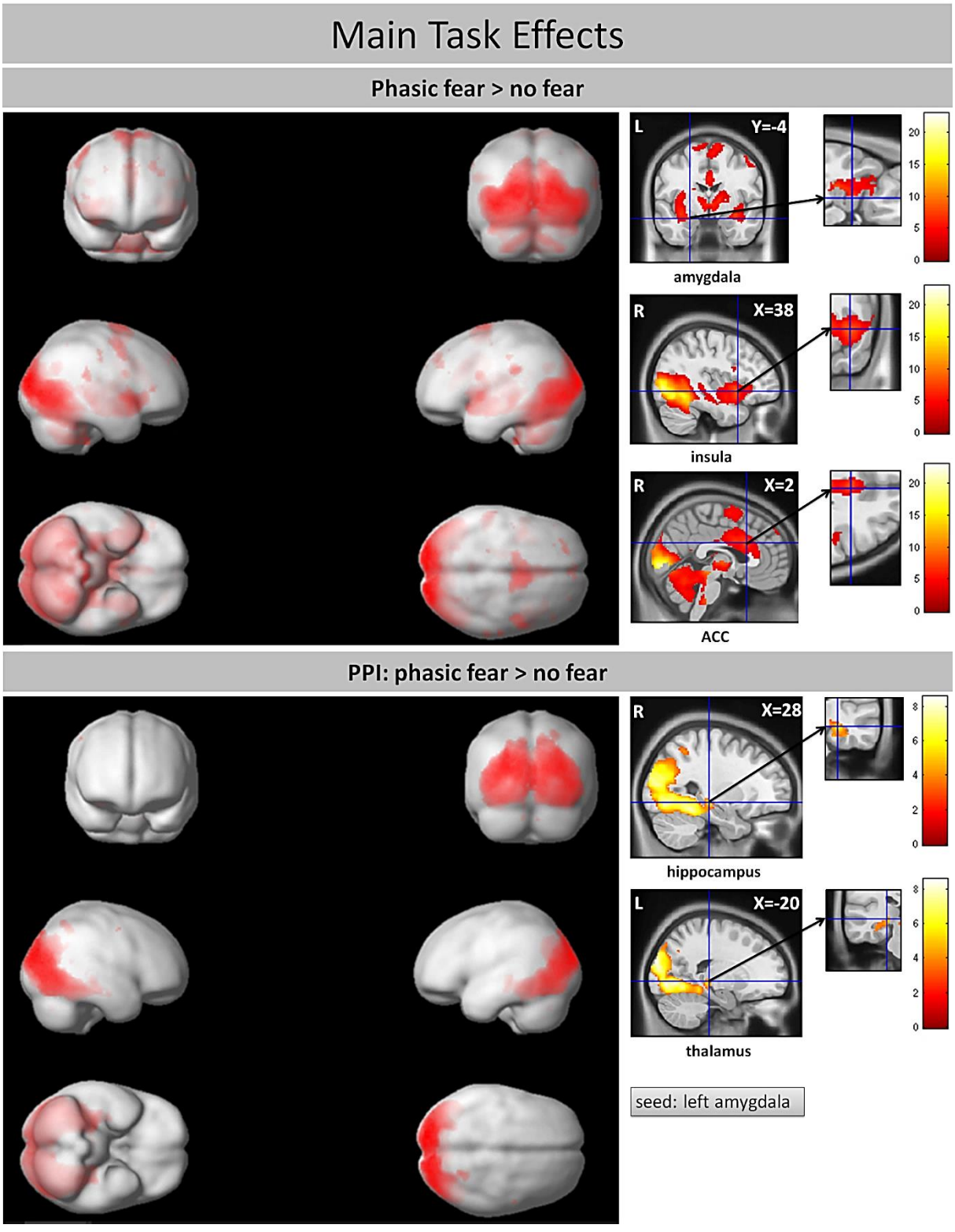

Figure 13. Main task effects and main task-based connectivity (PPI) for the contrast phasic fear > no fear of the SPF task. Left: overview of the whole-brain effect. Right: ROI peak voxels are displayed. Small volume corrections in pre-defined ROIs (FWE-corrected at $p < 0.05$) with a cluster-forming threshold of $p < 0.001$. ROI: region of interest; ACC: anterior cingulate cortex; PPI: Psychophysiological interaction.

3.3. PPI: task-based connectivity

If not explicitly indicated, results from ROI analyses are reported.

3.3.1. Main connectivity

The combined sample showed a stronger positive functional connectivity of the left amygdala (seed region) with bilateral hippocampus and bilateral thalamus based on the contrasted task conditions phasic fear > no fear (table 7, figure 13).

Whole-brain analyses additionally revealed a stronger task-based positive connectivity of the left amygdala with a cluster in the left SOG on that contrast (see table S6 in the appendix).

3.3.2. Group comparisons

All ROI group comparisons can be found in table 8 and figure 14, whole-brain results in table S7 in the appendix.

Primary outcome criterion (SPQ)

SPQ responders demonstrated higher task-based connectivity of the left amygdala with the right medial SFG based on the contrasted task conditions phasic fear > no fear. While connectivity was positive in responders, non-responders showed negative connectivity. No significant differences were found for the reverse contrast.

In the additional whole-brain analyses, the bilateral MTG, the right STG, and the bilateral medial SFG showed overall higher positive connectivity in responders based on that contrast, while connectivity in non-responders was negative. In one significant peak voxel in the left MTG, negative connectivity was seen in both groups, but responders showed less negative connectivity than non-responders. No significant differences in functional connectivity were found for non-responders > responders.

Secondary outcome criterion (BAT)

There were no significant differences in ROI analyses.

However, whole-brain analyses showed that BAT responders had a higher task-based positive connectivity of the left amygdala with the right calcarine sulcus, the left angular gyrus, and the right STG compared to non-responders, who showed negative connectivity. In the left MTG, negative connectivity was seen in both groups, but responders showed less negative connectivity than non-responders. No significant differences in task-based connectivity were found for non-responders > responders.

Within-session extinction

No significant group differences were found for high > low or vice versa, neither for ROI nor for whole-brain analyses.

Table 8. Functional and structural ROI group analyses for the contrast phasic fear > no fear and functional connectivity of the seed region based on the contrast phasic fear > no fear.

Contrast/group/region	side	voxels	x	y	z	*t*	*p*
SPF: Differential functional activation: phasic fear > no fear							
SPQ responder > non-responder						no significant differences	
SPQ non-responder > responder						no significant differences	
BAT responder > non-responder						no significant differences	
BAT non-responder > responder							
Medial superior frontal gyrus	R	68	6	30	60	4.84	0.002
Medial superior frontal gyrus	L	12	-2	26	60	4.32	0.012
Supplementary motor area	L	33	-2	24	60	4.20	0.013
Supplementary motor area	L	19	-10	10	48	3.96	0.026
Inferior frontal operculum	R	7	46	8	16	3.71	0.045
ws extinction high > low						no significant differences	
ws extinction low > high							
Inferior frontal operculum	R	22	46	18	16	4.13	0.013
Inferior frontal gyrus, pars triangularis	R	24	48	18	16	4.09	0.021
Inferior frontal gyrus, pars triangularis	R	3	58	22	10	3.85	0.040
Supplementary motor area	L	17	-10	6	64	3.76	0.044
Inferior frontal gyrus, pars orbitalis	R	2	40	30	-4	3.56	0.041
PPI: Differential functional connectivity: phasic fear > no fear[1]							
SPQ responder > non-responder							
Medial superior frontal gyrus	R	37	4	44	40	3.85	0.037
SPQ non-responder > responder						no significant differences	
BAT responder > non-responder						no significant differences	
BAT non-responder > responder						no significant differences	
ws extinction high > low						no significant differences	
ws extinction low > high						no significant differences	

Table 8 (continued).

Differences in grey matter volume (GMV)							
SPQ responder > non-responder						no significant differences	
SPQ non-responder > responder							
Hippocampus	R	15	23	-24	-8	4.11	0.006
Thalamus	L	12	-8	-6	11	3.58	0.024
BAT responder > non-responder							
Hippocampus	R	150	27	-11	-12	3.63	0.025
Amygdala	R	14	27	-9	-14	3.47	0.012
BAT non-responder > responder						no significant differences	
ws extinction high > low						no significant differences	
ws extinction low > high							
Middle frontal gyrus	R	124	30	54	24	4.07	0.028
Inferior frontal operculum	L	123	-59	9	8	4.06	0.008

[1] seed region: left amygdala, MNI coordinates [-24 -4 -18]
L: left; R: right; voxels: number of voxels per cluster; x, y, z: MNI coordinates; SPQ: Spider Phobia Questionnaire; BAT: Behavioral Avoidance Test; ws extinction: within-session fear extinction; SPF: Sustained and phasic fear paradigm; PPI: psychophysiological interaction. ROI peak voxels are given. Small volume corrections in pre-defined ROIs (FWE-corrected at $p < 0.05$) with a cluster-forming threshold of $p < 0.001$.

3.4. Brain morphometry

If not explicitly indicated, results from ROI analyses are reported and can be found in table 8 and figure 14, whole-brain results can be found in table S7 in the appendix.

3.4.1. Primary outcome criterion (SPQ)

SPQ non-responders had greater GMV in the right hippocampus and left thalamus than responders, there were no significant ROIs for the contrast vice versa.

Whole-brain analyses additionally revealed a cluster encompassing the left caudate nucleus, left thalamus, and left pallidum in non-responders (*t*-contrast: non-responders > responders), whereas the contrast responders > non-responders yielded no significant differences in GMV.

3.4.2. Secondary outcome criterion (BAT)

BAT responders showed greater GMV in the right hippocampus and the right amygdala than non-responders. There were no significant results for the contrast non-responders > responders.

3.4.3. Within-session extinction

Patients within the low extinction group demonstrated greater GMV in the right MFG and in the left IFO.

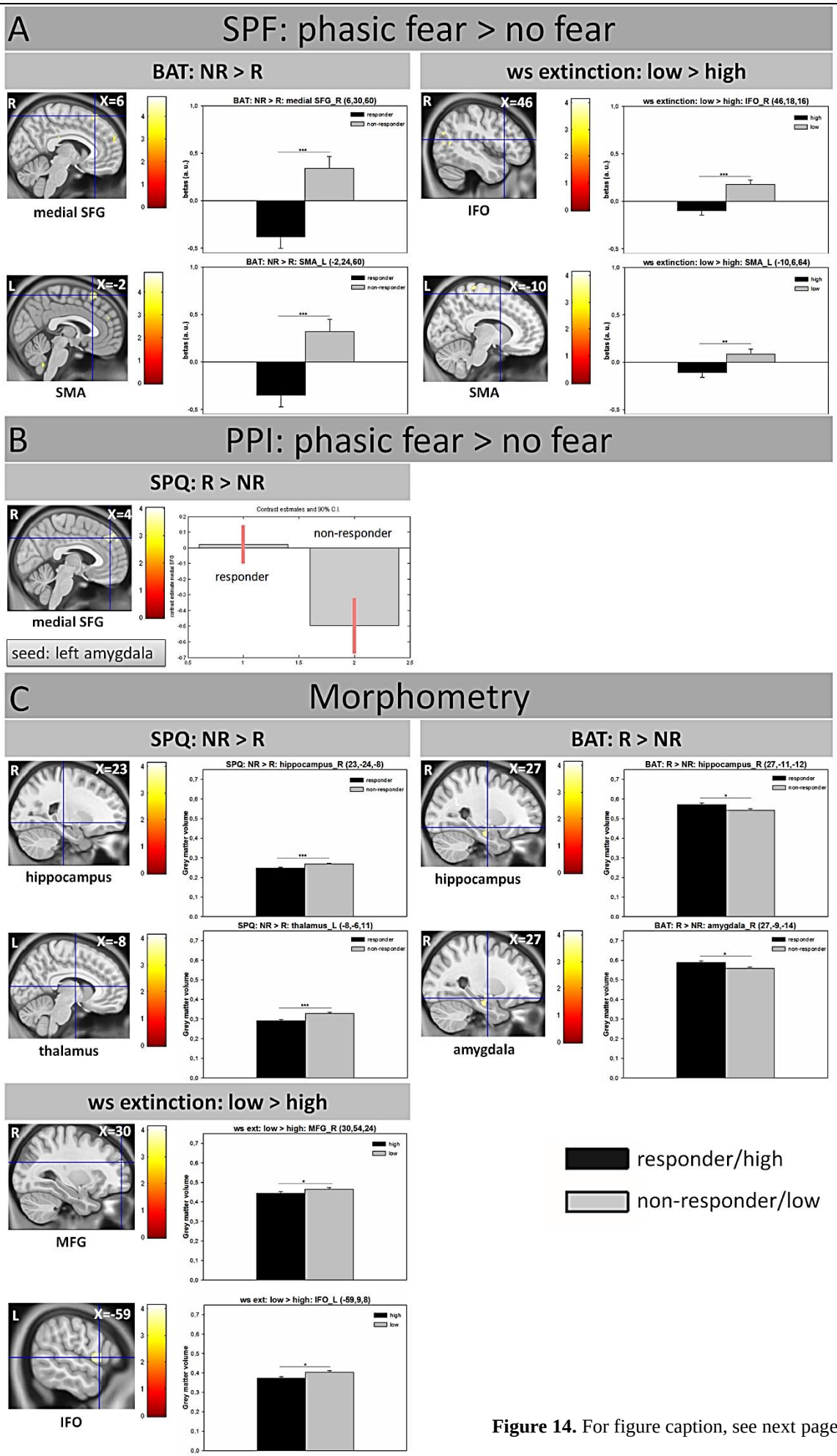

Figure 14. For figure caption, see next page.

Figure 14. Group comparisons according to analysis type and group classification. Peak voxels are displayed for small volume corrections in pre-defined ROIs (FWE-corrected at $p < 0.05$) with a cluster-forming threshold of $p < 0.001$. **A.** Functional activation differences in the SPF paradigm between classification groups for the contrast phasic fear > no fear. Beta values were extracted using a 5mm sphere, error bars indicate the SEM**. B.** Differences in task-based functional connectivity of the left amygdala as seed region between classification groups for the contrast phasic fear > no fear of the SPF paradigm. Contrast estimates plotted against the effect of interest show the effect of each regressor across the two groups with a 90% confidence interval (CI) in the selected voxel. **C.** Structural differences between classification groups. GMV bars indicate the mean proportion of GMV extracted with a 5mm sphere, error bars indicate the SEM. BAT: Behavioral Avoidance Test; NR: non-responder; R: responder; SFG: superior frontal gyrus; SMA: supplementary motor area; IFO: inferior frontal operculum; PPI: psychophysiological interaction; MFG: middle frontal gyrus; ROI: region of interest; GMV: grey matter volume; SEM: standard error of the mean. *** $p < 0.001$, ** $p < 0.01$, *$p < 0.05$.

4. Discussion

The present study employed a symptom provocation paradigm in patients with spider phobia before patients received a potent behavioral exposure in VR to identify neural pre-treatment moderators of treatment (non-)response. Patients were classified into different response groups via pre-defined outcome criteria. Differences distinguishing between these groupings were assessed by means of structural brain data, functional brain data, and task-based connectivity.

Two major effects were observed: first, on a neural level, fear processing in the whole sample was characterized by stronger activation in regions of the defensive system network, prefrontal, and visual areas; a similar picture emerged for task-based connectivity. Second, patients did indeed show pre-treatment differences in functional brain activation, task-based functional connectivity, and brain morphometry according to their later group classification based on treatment response. SPQ responders showed stronger visual activation and BAT responders exhibited a stronger task-based connectivity between the amygdala and the visual cortex, maybe indicating less visual avoidance and ergo stronger sensory processing in responders. Additionally, in SPQ responders the amygdala had a stronger task-based coupling with the mPFC, and other regions linked to regulatory processes. BAT non-responders and patients within the low ws extinction group, on the other hand, seemed to be characterized by enhanced activation in regions linked to threat processing and stronger fronto-parietal, dlPFC, and ventrolateral PFC (vlPFC) activation, possibly related to altered attentional processes or dysfunctional overcompensatory regulation mechanisms. Furthermore, SPQ non-responders showed greater GMV in regions of the defensive system network.

4.1. Neural networks of fear processing in spider phobia

In line with expectations, we observed stronger activation in the whole sample within regions associated with fear, threat processing, and defensive mobilization (e.g. amygdala, hippocampus, thalamus, SMA) in spider phobia patients while viewing spiders compared to neutral stimuli. Similar results have been observed in previous studies in spider phobia (e.g.

Åhs et al., 2009; Del Casale et al., 2012; Peñate et al., 2017a; Wiemer et al., 2014). Rating data further clearly showed that spider pictures were perceived as significantly more unpleasant than neutral ones.

The left amygdala showed increased functional coupling with the bilateral hippocampus and bilateral thalamus for the phasic fear > no fear condition. The interaction between amygdala and hippocampus is involved in fear memory (Raber et al., 2019) and enhanced functional coupling between amygdala and hippocampus is associated with fear memory retention (Hermans et al., 2017; Pape & Pare, 2010; Smith, Stephan, Rugg, & Dolan, 2006). Evidence suggests that arousal-mediated amygdala-hippocampal connectivity is the link between amygdala activation and phobic memory (Åhs et al., 2011). The degree of amygdala activation during encoding of emotionally arousing stimuli is associated with the consolidation to long-term memory, i.e. emotionally significant memories are better remembered (McGaugh, 2004). Regions within the hippocampus trigger contextual threat memories (Milad, Wright, et al., 2007), maybe recalling previous episodes of phobic fear in the sense of a CR to the phobogenic stimulus (Schaefer, Larson, Davidson, & Coan, 2014).

Additionally, we found heightened activation in visual areas and congruously, increased functional coupling between the left amygdala and occipital cortices modulated by the perception of the phasic fear condition, corroborating previous studies using visual stimulation in spider phobia (Åhs et al., 2009; Lange et al., 2019; Schienle et al., 2007; Wiemer & Pauli, 2016; Zilverstand, Sorger, et al., 2017). The amygdala has rich feedback projections within the visual ventral stream (Amaral et al., 2003). Fear-elicited activation of the amygdala can be mediated through the visual cortical pathway (Nakataki et al., 2017). Visual perception can be changed by emotional experiences, resulting in the prioritization of sensory information associated with threats. Although these emotional biases have been extensively researched by both basic and clinical scientists, their underlying mechanisms are still not fully clear. Evidence suggests that short-term plasticity in primary visual regions, including changes in network connectivity or synaptic weights, could mediate the formation of perceptual biases to threat in a similar way as assumed for attentional resources (Keil, Stolarova, Moratti, & Ray, 2007; Thigpen, Bartsch, & Keil, 2017; Vuilleumier, 2015). There also seems to exist a positive linear relationship between the arousing quality of visual stimuli, amygdala activation, and visual cortices activation (Sabatinelli, Bradley, Fitzsimmons, & Lang, 2005).

Initial responses in the human visual cortex are sensitive to stimuli associated with emotionality. Emotionally relevant stimuli might therefore lead to enhanced activation in the visual cortex, maybe by interacting with sub-cortical structures. As a function of previous

experience and context, these responses are amplified to enhance emotional perception, thereby presumably allowing the emotional brain to constantly adapt to key features of relevant stimuli. Constantly adapting and optimizing the visual system may ergo be beneficial for efficiently reacting to potentially threatening stimuli at the earliest stages possible (Keil et al., 2007).

Through bottom-up mechanisms, the amygdala facilitates automatic perceptual processing by directing or biasing attention (LeDoux, 2000). The involvement of the amygdala in the processing of threat-relevant information in SP plays a role in sustained vigilance for threat, a central characteristic of SP. Moreover, the magnitude of amygdala responsiveness seems to be specifically potentiated by sustained hypervigilance for threat. Deviations in the vigilance system therefore seem to be critically involved in psychopathology (Lipka et al., 2011) and may be potentiated by a perceptual bias indicated by enhanced visual processing.

Activation in the SMA and other motor regions provides the organism with motor readiness to support a fight-or-flight response (Åhs et al., 2009; Goossens et al., 2007). Heightened activation in the ACC may reflect greater salience, enhanced sensitivity, or a lower perceptual threshold for detecting threat, ergo directing attention more easily towards these cues (Britton et al., 2009).

Phobic patients show attention biases to threat (Aue & Okon-Singer, 2015). However, the neural underpinnings and mechanisms at the basis of attentional biases to threat are still not fully understood. The amygdala is assumed a key player in biasing attention to threat, resulting in hypervigilance and/or attention biases. Sustained, inappropriate biases may be a consequence of stress-induced amygdala sensitization (Hur, Stockbridge, Fox, & Shackman, 2019). Prefrontal regions, besides insula, limbic areas, and (hypo-)thalamic areas, are also involved in threat processing. Activation of the MFG and SFG has been observed in high threat situations (Patrick et al., 2019). The SFG has also been observed to be involved in attention and attention shifting (Nagahama et al., 1999). Ergo, the SFG might be involved in active tasks in general, independent of the content (Patrick et al., 2019). Several studies in spider phobia also found enhanced activity in prefrontal areas in response to phobic stimuli (Paquette et al., 2003; Schienle et al., 2007; Straube, Mentzel, & Miltner, 2006; Wiemer et al., 2014; Zilverstand, Sorger, et al., 2017) like we did. Straube et al. (2006) concluded, that the dmPFC is rather related to direct threat evaluation, in contrast to the amygdala which processes stimuli automatically, and therefore needs sufficient attentional resources. In another study from the same working group, it was also revealed that phobia-related vs. phobia-unrelated words elicited inter alia heightened activation in the dlPFC in spider phobics, while in HC no such effect emerged (Straube, Mentzel, Glauer, & Miltner, 2004). It has also been suggested that

enhanced prefrontal activation during symptom provocation could mirror attempts to downregulate the emotional response (Paquette et al., 2003) or higher order cognitive processes (Zilverstand, Sorger, et al., 2017). However, other studies found phobic patients to show decreased activation in the mPFC during symptom provocation (Hermann et al., 2009). Further studies are needed to clarify the role of prefrontal areas in phobic fear networks, since results are still inconsistent.

In a recent meta-review of fMRI studies in small animal phobia by Peñate et al. (2017), the random-effects model demonstrated a high overall effect size for limbic and frontal sites, which the authors interpret as support for a possibly existing double processing pathway of phobogenic stimuli. While a rapid processing pathway would recruit limbic areas, the slow pathway would integrate both limbic and prefrontal regions. This theory can be well integrated into the high and low road model from LeDoux (1994). These different pathways in SP may be modulated and potentiated by aberrant attentional processes like sustained hypervigilance. Heightened bottom-up amygdala (fast pathway, facilitating attention) and top-down prefrontal activation (slow pathway, aberrant attentional and cognitive control) might represent biased attentional processes, while heightened visual activation may indicate a perceptual bias. However, the exact neural pathway engaged in the pathological processing of phobia-relevant information remains unknown (Nakataki et al., 2017) and should be further elucidated by future studies.

4.2. Group differences and moderators of treatment outcome

4.2.1. SPF

Although there were no ROI-based differences between SPQ responders and non-responders unlike we expected, whole-brain results showed a stronger activation in the left lingual gyrus in responders for the contrast phasic fear > no fear. This might reflect reduced visual avoidance in responders, leading to a deeper perceptual processing of the phobic stimuli. Visual avoidance of phobogenic information occurs during controlled processing in phobic patients and may be due to heightened fear circuitry activation signaling potential threat. It may serve as a maladaptive mechanism to down-regulate cognitive risk evaluations about the fear-related stimuli, because phobic patients may lack efficient regulation and coping strategies. An eye-tracking study showed, the greater the visual avoidance of spiders, the higher the activation in fear circuitry structures like the amygdala (Aue, Hoeppli, Piguet, Sterpenich, & Vuilleumier, 2013). Another study found spider phobics, compared to HC, to show reduced activity in the visual cortex in anticipation of phobic stimuli, which was interpreted as a neural sign of anticipatory visual avoidance (Wik, Fredrikson, & Fischer, 1996). Visual avoidance might

signify a deficient fear regulation, trying to de-escalate the fear response which prevents extinction or habituation processes. The exact conditions leading to visual avoidance and its consequences are, however, not fully clear. There may be an individual degree of deploying visual avoidance among phobic patients which is again dependent on the given situation (Aue et al., 2013).

Interestingly, a study examining treatment outcome of exposure-based CBT in spider phobics found stronger activation in a cluster in the lingual gyrus directly after therapy to be predictive of positive long-term therapy outcome (Hauner, Mineka, Voss, & Paller, 2012). Of note, an avoidant attention bias compared to a vigilant attention bias to threatening stimuli at pre-treatment was associated with poorer CBT response post-treatment in SAD (Price, Tone, & Anderson, 2011). Thus, if individuals do show individual patterns of vigilance and avoidance which have predictive value for treatment response, knowing these patterns in advance could be beneficial for specifically targeting them either before or throughout therapy . Taken together, less visual avoidance may signify better or more adaptive emotion regulation capacities in responders which is later beneficial throughout exposure, since less avoidance behavior allows extinction learning to take place more efficiently. However, empirical evidence is mixed and incoherent, with results showing both biases towards and away from threat-related stimuli in spider phobia (Fox, Zougkou, Ashwin, & Cahill, 2015).

For both BAT non-responders and patients within the low ws extinction group, a similar picture emerged for the contrast phasic fear > no fear: heightened activation in defensive network regions like the SMA and IFO may represent enhanced threat processing and active avoidance. Stronger fronto-parietal, dlPFC, and vlPFC activity may reflect aberrant attentional processes, like hypervigilance or a difficulty to disengage from phobic stimuli alongside with enhanced threat-related processing. It could also mirror an dysfunctional overcompensation of top-down regulation, attempting to decrease the excessive emotional response, therefore requiring greater cognitive effort (Duval et al., 2015). In SP, a lack of top-down control efficiency may give initial bottom-up responses more power. However, maybe these bottom-up responses in SP are so potent that even an intact top-down control cannot suppress them. Emotion regulation ergo represents competing bottom-up and top-down processes, with the amygdala and prefrontal cortex as key players (Kim et al., 2011). While the dlPFC may be more linked to regulating cognitive processes like attention, the vlPFC may rather signal salience and thereby indicating the need to regulate (Kohn et al., 2014). SP seems to be characterized by a lack of efficient automatic regulatory mechanisms and by deficits in effortful cognitive control of emotional responses. This may be a display of diminished inhibitory prefrontal abilities (Del

Casale et al., 2012). It is thought that phobics do however use top-down control mechanisms as attempt to downregulate exaggerated responses, but that they use ineffective strategies (Aue et al., 2015), like attentional or visual avoidance.

Although functional studies in SP are quite common, differences in methodology or conceptualizations are still problematic. Therefore, results may often be interpretable within the specific methodological and conceptional framework only, which might account for inconsistent or even contradictory results between studies.

4.2.2. PPI

In SPQ responders, the left amygdala showed stronger task-based coupling with the medial SFG and temporal cortices. Evidence suggests that the magnitude of crosstalk between the amygdala and the mPFC is a crucial factor regarding behavioral outcomes of reported anxiety. That is, the stronger the coupling, the better the outcome (Kim et al., 2011). The MTG, angular gyri, and visual cortices have been associated with the negative prediction error, meaning that an expected outcome is less than predicted or does not occur at all. The negative prediction error is an initializing trigger to feedback loops conferring fear extinction (Spoormaker et al., 2011).

Although we did not find differences in expected ROIs, whole-brain results revealed a stronger task-based functional connectivity between the left amygdala and the calcarine sulcus, angular gyrus, and temporal cortices in BAT responders. The stronger synchronization of the amygdala and the visual cortex might reflect a deeper processing of phobogenic visual information which adds additional evidence towards our hypothesis of reduced visual avoidance in responders. STG and angular gyrus are also associated with the execution of emotion regulation processes initiated by frontal areas (Kohn et al., 2014; Wager, Davidson, Hughes, Lindquist, & Ochsner, 2008), ergo this could represent a better pre-treatment ability to regulate the emotional response in responders.

Taken together, responders may be equipped with pre-treatment prerequisites for achieving a better treatment response later on. For instance, a stronger functional coupling between the amygdala and the mPFC, STG, and angular gyrus may be beneficial to regulatory processes, while a stronger coupling with visual cortices may be linked to deeper perceptual processing and reduced visual avoidance.

Although a PPI is an insightful method, they are employed rather rarely. Most connectivity studies do not incorporate the task condition and by doing so - may miss on important task-related information. However, the question of the direction of influence remains

unclear using PPIs, therefore, dynamic causal modelling (DCM) may represent a promising alternative for future studies to get more information about direction and causality.

4.2.3. Brain morphometry

As expected, SPQ non-responders had greater GMV in regions involved in the fear circuitry and the processing of fear (hippocampus and thalamus). Greater GMV in the hippocampus and the thalamus may represent a stronger fear memory and enhanced sensory fear processing. This may be associated with worse treatment response, in that a particularly strong fear memory may be harder or may take longer to be extinguished.

However, contrary to the SPQ results and our expectations, BAT responders also showed greater GMV in the right hippocampus and the right amygdala. Exploratory data analyses to check if the contrary effect may result from individuals switching group classifications showed that this was not the case. Data indicated that this effect was mainly driven by a few outliers, though. Unfortunately, other structural studies in SP have also yielded contradictory results and to our best knowledge, there are no studies on structural moderators of treatment response in SP so far. This makes it difficult to draw a conclusion from our results at this point. Further structural studies are needed to address this topic.

Patients within the low ws extinction group had greater GMV in the right MFG and the left IFO. This mirrors functional results and therefore, may also be associated with aberrant emotional attention in spider phobia.

In general, studies investigating deviations in brain structure related to SP are still scarce. More insight in structural alterations is, however, of high importance since structural changes may underlie functional aberrations or vice versa. Moreover, there may also be decisive changes and differences in WM, not only GM (Hilbert, Evens, Maslowski, Wittchen, & Lueken, 2015). Future studies should increasingly use morphometric units of analysis to get an integrated picture.

4.3. Limitations

In the present study, exposure treatment was realized using VR. Therefore, we cannot ensure that treatment effects are not method-specific and would have been the same, or comparable, to an in vivo exposure or the like. Furthermore, the BAT which was part of the diagnostics, but not part of the treatment itself, may have had additional exposure effects which cannot be clearly disentangled from the effects of the VRET.

Due to the main research question regarding the moderating effect of pre-treatment characteristics on treatment outcome in spider phobia, a control group was not necessary nor target-aimed. Nevertheless, a control group could have been beneficial in further elucidating

alterations in phobic fear processing compared to HC, or resp. non-phobic (fear) processing.

Since we only examined differences in neural signatures within a group of clinically diagnosed spider phobics during symptom provocation, this potent paradigm expectably yielded a very strong responding in all patients. These very strong activations may have led to ceiling effects, making it hard or maybe even impossible to detect subtle differences due to group classification. Moreover, we used a block-design, an event-related design may have been more suitable to detect subtle group differences (Goossens et al., 2007). Furthermore, this experimental design did not allow for examining the temporal dynamics of vigilance and avoidance patterns or to assess concomitant viewing behavior, making a distinction from early and late processes impossible at this point.

One has to keep in mind the difference between remission vs. reduction, since most of our patients did show a symptom severity reduction, but not yet full-remission. This may also account for less pronounced differences between the response classifications, since those classified as responders did, however, show a significant reduction of symptom severity according to our pre-defined outcome criteria, but were not automatically free of diagnosis.

Group classification according to the SPQ, BAT, and the ws extinction showed overlap of at least 50% or higher between the resulting groups, one must keep that in mind while interpreting the groups as different entities, since they are not fully independent and may reflect different underlying constructs. The SPQ and BAT served as outcome measures, with the SPQ assessing a more cognitive component via self-report, while the BAT assesses the behavioral component. The ws extinction, however, is not as an outcome measure per se but can be considered as a process measure throughout the exposure.

4.4. Conclusions and future directions

The present study supports the idea of existing pre-treatment neural signatures exerting a moderating influence on treatment response towards behavioral exposure in spider phobia. Pre-treatment differences related to regulatory, attentional, and perceptual processes may have predictive value for treatment outcome. Reduced (visual) avoidance tendencies and ergo, a deeper processing of phobogenic stimuli as well as a stronger synchronization of the amygdala and regions associated with regulatory/inhibitory processes may represent prerequisites for later positive exposure treatment outcome. On the other hand, stronger defensive network activation, active avoidance, stronger aberrant regulatory and/or attentional processes, or a particularly strong fear memory may be associated with lesser treatment success. The predictive value of neural markers and their benefit for improving and individualizing treatment approaches is still

neither well-researched nor optimally translated to the clinical level. Thus, our results should be replicated by future studies.

While stronger activation in limbic circuits may demonstrate pathophysiological emotional processes, enhanced activation in fronto-parietal circuits may represent biased attentional influences (Vuilleumier & Driver, 2007). Attentional and visual processing is influenced by emotional arousal and valence (Madan, Bayer, Gamer, Lonsdorf, & Sommer, 2018). Previous studies have described a vigilance-avoidance pattern in spider phobia, with an initial direction of attention towards fear-related stimuli, which is then followed by avoidance (Pflugshaupt et al., 2005). While the early vigilance may contribute to amplify anxiety, later avoidance may contribute to the maintenance of fear (Reese, McNally, Najmi, & Amir, 2010).

Targeting attentional biases in individuals with an attention training (attention bias modification training, ABM) may support an increase in cognitive control over attention and in this way, may improve emotion regulation skills (McNally, 2019). While ABM could be applied for modifying initial hypervigilance, exposure therapy could target avoidance and ergo, complement each other (Reese et al., 2010). A study in spider fearful individuals showed that pre-training individual differences in attentional bias predicted the success of the training, indicating that not all participants responded equally well (Fox et al., 2015). Knowing already prior to treatment who will likely benefit from ABM would hence be a great advantage. However, the efficacy of ABM in general (McNally, 2019) and in spider phobia is ambiguous, and ABM may be more suitable for disorders that are not as clearly stimulus-bound as in spider phobia (Reese et al., 2010; Van Bockstaele et al., 2011).

Hence, there are still gaps and inconsistencies in our understanding and the current state of research. Most recently, personalized medicine approaches are accumulating to detect individual pre-treatment markers of clinical response. Nevertheless, most studies are limited by their group-based approach that does not allow guiding clinicians to select an adequate treatment for individual patients as a crucial prerequisite for translating personalized treatment approaches to clinical care. To ensure and evaluate the robustness and generalizability of moderators, future studies would benefit from explicitly including an external (e.g. out-of-sample) cross-validation protocol. Beyond the proof of efficacy for the average patient, current research on factors moderating the outcome of exposure-based CBT calls on strengthening the perspective on personalizing treatments (Richter, Pittig, Hollandt, & Lueken, 2017).

IV DISCUSSION AND OUTLOOK

Fear conditioning and extinction enable the organism to adapt to its changing environmental conditions, thereby avoiding potential harm and maximizing survival. They ergo represent fundamental emotional-associative learning mechanisms based on evolutionary roots. Aberrations in these very learning mechanisms can result in an impaired ability to adjust and adapt behavior to environmental challenges in a flexible manner. This again can lead to inadequate and blunted fear responses due to alterations like enhanced fear conditioning or an attenuated extinction recall, as seen in the ADs. Hence, deviations in fear conditioning and extinction processes are considered a key pathomechanism in the development and maintenance of ADs (Lueken & Maslowski, 2012). This thesis aimed at shedding additional light onto deviant processes of fear (un-)learning as a transdiagnostic feature of psychopathology in ADs.

1. Summary of results

Basic emotional-associative learning processes like fear conditioning and extinction are highly relevant to the development and maintenance, but also to the treatment of ADs. Taking this crucial and pivotal role into account, we focused on different applications of the same fundamental principle by using two example cases of ADs from two different multicenter trials, the "Panic-Net" (BMBF) and the CRC-TRR58 "Fear, Anxiety, Anxiety Disorders" (DFG).

First, we targeted deficits in basic mechanisms of fear learning, extinction, and its recall as a function of psychopathology in PD patients in comparison to HC. Second, the clinical analogue to extinction, i.e. exposure-based therapy, and pre-treatment patient characteristics exerting a moderating influence on this essential learning process later on were examined using multimodal functional and structural neuroimaging in spider phobia.

1.1. Emotional-associative learning deficits in PD

A differential fear conditioning and delayed extinction paradigm was employed on three consecutive days in PD patients to unravel neural networks involved in fear acquisition, extinction, and recall of fear-related memories. By doing so, we aimed at gaining more insight into altered brain activation patterns as a function of PD and to closer match fear conditioning and extinction protocols based on animal research to the clinical level. A novel paradigm with distinct overnight consolidation phases between fear conditioning, extinction training, and recall was used. Explicitly including a distinct extinction recall phase aimed at gathering more knowledge about deficits in extinction recall in PD, since studies are still scarce or not available at all. Extinction recall bears, however, a high translational value for better understanding the problem of clinical relapse. Due to ethical aspects, experimental research will always be limited

in modeling clinical relapse (Scheveneels, Boddez, Vervliet, & Hermans, 2016). Therefore, translational laboratory research on deficits in extinction recall as an analogue to relapse is an even more important proxy-measure (Vervliet et al., 2013).

Two major effects were observed: first, PD patients were characterized by enhanced activation in networks subserving fear conditioning such as the amygdala or insula, particularly during the initial trials of the acquisition phase, possibly indicating accelerated fear conditioning processes. Second, patients showed attenuated recall of extinction memories as indicated by sustained activation of fear circuitry networks encompassing the insula, IFO, and IFG.

1.2. Moderators of treatment response in spider phobia

A symptom provocation paradigm was employed in patients with spider phobia before patients received a potent behavioral exposure in VR. We aimed to identify neural pre-treatment moderators of treatment (non-)response and to characterize fear processing in spider phobia. Patients were classified afterwards into different response groups via pre-defined outcome criteria. Differences distinguishing between these groupings were analyzed by means of structural brain data, functional brain data, and task-based connectivity. Given the high amount of non-responders towards exposure-based CBT, identifying moderators of treatment outcome before starting a potentially ineffective therapy would be of great advantage to clinicians and patients.

Two major effects were observed: first, on a neural level, fear processing in the whole sample was characterized by stronger activation in regions of the defensive system network, prefrontal, and visual areas; a similar picture emerged for task-based connectivity. Second, patients differed in functional brain activation, task-based functional connectivity, and brain morphometry according to their later group classification based on treatment response. SPQ responders showed stronger visual activation and BAT responders exhibited a stronger task-based connectivity between the amygdala and the visual cortex, maybe indicating less visual avoidance and a stronger sensory processing in responders. Additionally, in SPQ responders the amygdala had a stronger task-based coupling with the mPFC and other regions linked to regulatory processes. BAT non-responders and patients within the low ws extinction group, on the other hand, seemed to be characterized by enhanced activation in regions linked to threat processing, and stronger fronto-parietal, dlPFC, and vlPFC activation, perhaps indicating altered attentional processes or dysfunctional overcompensatory regulation mechanisms. Furthermore, SPQ non-responders showed greater GMV in regions of the defensive system network.

1.3. An integrative model of enhanced defensive reactivity and deficient top-down control mechanisms in anxiety disorders

Although PD and SP both belong to the group of ADs, they represent different anxiety phenotypes. PD and SP differ in their threat predictability that is associated with pathological states of anxiety in both disorders. While PD is more related to sustained anxiety, due to unpredictable disorder-specific threat, SP is characterized by a phasic fear response to predictable threat (Klahn et al., 2017). Despite differing in many aspects, they also share commonalities which pertain to all ADs. In both disorders, fear conditioning and extinction processes are thought to play a central role in their development, maintenance, and finally, their treatment.

Looking beyond the characteristic features of the two different ADs and independent of the different study designs and paradigms used, the following hypothetical model (see figure 15 for a schematic representation) tries to integrate the findings from both studies on a broader level, and to allocate them transdiagnostically within the RDoC framework (since the RDoC approach will be further elucidated and discussed in chapter 3.3 “The age of RDoc”). Two core aspects can be hypothesized from our data:

1) Both studies corroborate the central role of the amygdala and related fear circuitry structures, supporting the role of a hyperactive defensive system network in patients with ADs. PD patients showed an accelerated fear acquisition and stronger amygdala activation during acquisition than controls. Moreover, fear circuitry was stronger recruited during extinction recall. In spider phobia, overall, non-responders also showed stronger fear circuitry activation and greater GMV in related structures including the hippocampus, potentially linked to a stronger fear memory, than in responders.
2) Furthermore, results could be interpreted as potential reflection of deficient emotion regulation processes and top-down control in ADs. In PD, this deficit in emotion regulation capacities may be reflected by an attenuated extinction recall, thereby impairing the long-term retrieval of extinction, a form of emotion regulation. In spider phobia, those patients classified as responders, may take advantage of more effective emotion regulation strategies or a stronger connectivity between the amygdala, regulatory, and visual regions, i.e. they may process more deeply and avoid less, thereby allowing extinction learning to take place more easily than in non-responders. A stronger coupling between the amygdala and regulatory/inhibitory regions like the mPFC may represent a pre-treatment prerequisite for a better treatment outcome later on, since the mPFC is also involved in emotional inhibition and extinction (Phelps et al., 2004).

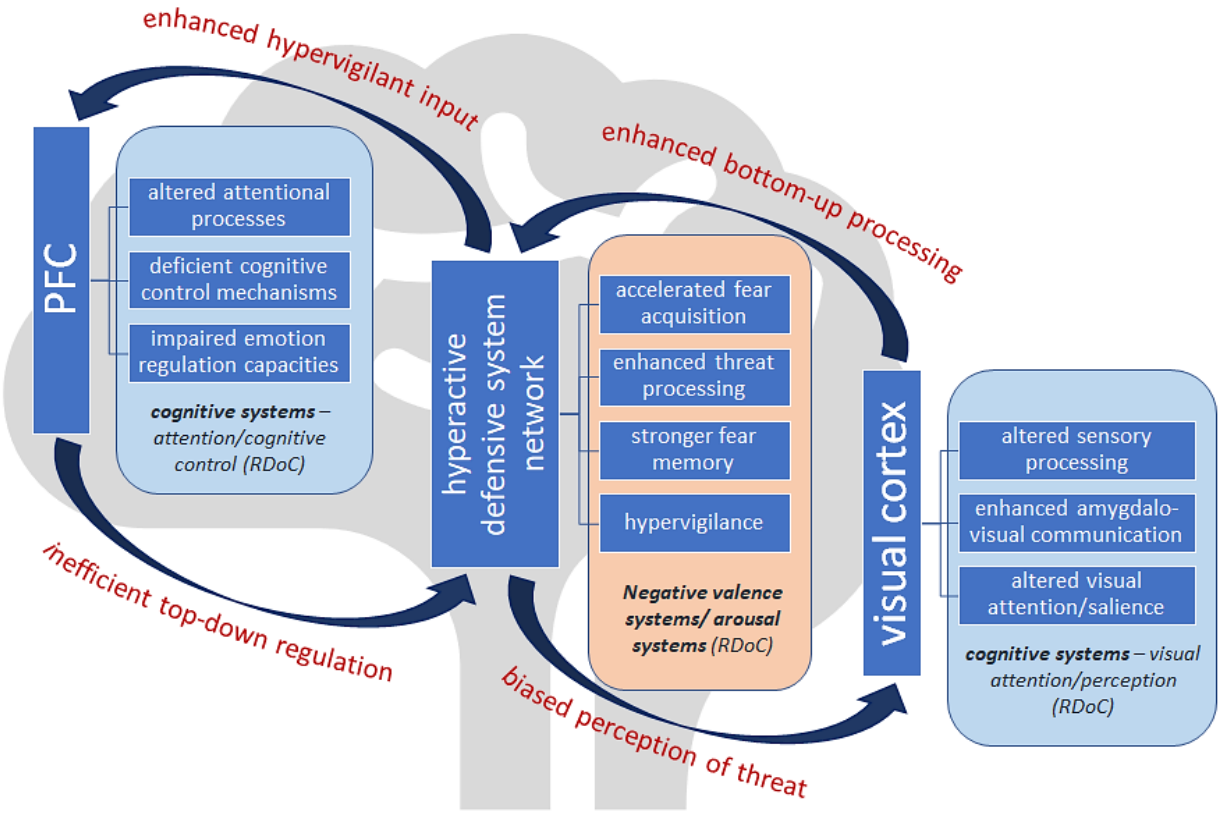

Figure 15. Schematic representation of an integrative model of findings. A hypothesized model trying to integrate findings from both studies on an overarching simplistic level, and to allocate them within the RDoC framework. AD patients seem to have an hyperactive defensive system network. Emotion regulation processes and top-down control capacities may be impaired in ADs, either by ineffective overcompensatory mechanisms or by using inefficient regulation strategies. This may be further influenced by altered attentional and sensory processes. This might lead to a disrupted interaction and imbalance between top-down and bottom-up processes. All these processes are assumed to be mutually dependent and intertwined, presumably reinforcing each other. PFC: prefrontal cortex; RDoC: research domain criteria.

Increased prefrontal activation might probably signify an increased need 1) to regulate due to enhanced input from hyperactive defensive system networks and hypervigilance, 2) to suppress behavioral tendencies or, 3) could reflect ineffective attempts of down-regulation. It is assumed that the neural mechanisms involved in fear inhibition, emotion regulation, and fear extinction overlap (Hartley & Phelps, 2010). This underlying circuitry might be altered in ADs, and in combination with a hyperactive defensive system network, may culminate in a fundamental deficient functioning in automatic and intentional emotion regulation processes. A reduced capacity to regulate emotional responses represents a common impairment across mental disorders, and evidence suggests deficits in emotion regulation as central to both the development and maintenance of psychopathology (Sloan et al., 2017; Zilverstand, Parvaz, & Goldstein, 2017).

Enhanced prefrontal and fronto-parietal activation patterns may also reflect attentional biases, maybe further hampering emotional regulation due to difficulties in disengaging from

threatening stimuli and thereby limiting top-down cognitive control capacities. This might lead to enhanced bottom-up attention-driven sensory processing as mirrored by enhanced visual activation, which could again act on amygdala activation by neural backprojections and via stronger functional coupling between visual regions and the amygdala. Attentional biases are linked to amygdalar activity, as has been observed in other ADs. In SAD for instance, initial hypervigilance as indicated by reflexive attentional orienting (gaze direction) towards phobogenic stimuli (eyes) was observed, speaking for biased mechanisms of early attentional exploration of phobia-relevant cues which might play a role in developing and maintaining SAD (Boll, Bartholomaeus, Peter, Lupke, & Gamer, 2016). Amygdala activation has been associated with the initiation of reflexive gaze shifts towards fearful eyes in healthy individuals (Gamer & Büchel, 2009), and biased automatic shifts in SAD may be linked to amygdala hyperactivation (Boll et al., 2016). Attentional disengagement from fearful facial stimuli in healthy subjects leads to a decrease in amygdala responding, corroborating the influence of attentional processes on amygdala activation (Brassen, Gamer, Rose, & Büchel, 2010).

It is hypothesized that the interaction between bottom-up and top-down processes is disrupted in ADs, especially between attention and control. While attentional salience is boosted, executive control is attenuated (Hur et al., 2019). Evidence points to attentional biases as causal factors in eliciting and maintaining anxiety, rather than representing an epiphenomenon (Browning, Holmes, Murphy, Goodwin, & Harmer, 2010). Current research hints at a deficient functioning of executive control as the core attentional problem linked to (pathological) anxiety. While cognitive biases show content-dependency, cognitive deficits are independent of content and may thereby constitute are more basic feature of psychopathology in general. These deficits in cognitive control over attention may then result in further problems inhibiting attention to threat. For instance, in spider phobics threat cues may capture attention and deficient executive control mechanisms may lead to a proneness of stimulus-driven capture, to difficulties in disengaging attention from threat cues, or both (McNally, 2019).

Enhancing executive control over attention might therefore lead to more effective emotion regulation capacities and may decrease anxiety proneness. Reducing attentional biases and hypervigilance with an attention training (e.g. ABM) could aid to increase cognitive control over attention and thereby ameliorate emotion regulation skills (McNally, 2019). Enhancing emotion regulation capacities could be further targeted via enhancing extinction learning (see chapter 3.1. “Enhancing extinction learning”) and diminishing the use of maladaptive emotion regulation strategies like avoidance, for example via exposure treatment. Patients could also be further provided with learning efficient intentional emotion regulation strategies like cognitive

reappraisal to deliberately counteract deficits in (automatic) emotion regulation. Treatments targeting emotion regulation skills and cognitive control capacities could be added to disorder-specific treatment components, thereby maximizing chances for success.

Neurofeedback (NF) is a non-invasive method to purposefully alter brain function via real-time monitoring of actual brain states and hence, provides a powerful option for both neuroscience and the treatment of mental disorders (Hampson, Ruiz, & Ushiba, 2020). Using real-time-fMRI-NF could show that healthy individuals are capable of regulating 1) their brain activation in regions linked to emotion regulation, 2) their brain activity in terms of prefrontal-limbic connectivity, as well as 3) their brain activity in individually navigated ROIs (Linhartová et al., 2019). A recent study demonstrated that amygdala down-regulation can also be successfully trained using real-time-fMRI-NF in healthy subjects (Herwig et al., 2019). Evidence further suggests that NF can decrease anxiety in AD patients and may ergo represent a promising tool for enhancing emotion regulation (Linhartová et al., 2019), whose potential benefits should be evaluated in future studies.

2. Limitations

2.1. Methodological considerations

The behavioral exposure presented in this thesis was delivered using a one-session VRET. Several studies showed efficacy of one-session exposure therapy in SP (Andersson et al., 2009, 2013; Öst, 1996; Vika, Skaret, Raadal, Ost, & Kvale, 2009), superiority of five versus one session could not be proven (Öst, Brandberg, & Alm, 1997; Öst, Hellström, & Kåver, 1992; Vika et al., 2009), and on a meta-analytical base, multi-sessions were only marginally superior compared with one-session therapies (Wolitzky-Taylor, Horowitz, Powers, & Telch, 2008). Evidence for the efficacy of VRET is comparable to exposure-based CBT in vivo (Emmelkamp, Bruynzeel, Drost, & van der Mast, 2001; Gilroy, Kirkby, Daniels, Menzies, & Montgomery, 2000, 2003) and the acceptance and commitment of patients is even higher as for exposure-based CBT in vivo (Garcia-Palacios, Botella, Hoffman, & Fabregat, 2007). Still, interpreting the results of these studies, one has to bear in mind the often small sample sizes, a shortage of adequate control groups, and in general, a lack of randomized controlled trials (Page & Coxon, 2016). However, as technical aspects are improving, VRET seems to be a good alternative to exposure-based CBT in vivo (Botella, Fernández-Álvarez, Guillén, García-Palacios, & Baños, 2017), when therapist, as well as patient, keep in mind the following traps: 1) cognitive avoidance in the form of “focus on unrealness” during exposure, 2) possibly limited action

radius for the patient, 3) the need to actively change procedure and circumstances and, 4) the translation into daily life of the patient.

Both studies in this thesis used (f)MRI as a means of analysis. The MRI scanner itself has several stress-eliciting and fear-evoking properties. The claustrophobic and noisily environment, discomfort, a low sense of control, and for many individuals, the novelty of the situation and related worries of the innocuousness, can lead to anxiety-related reactions. These unfavorable experiences may result in impaired data quality or even premature termination of scanning. The anticipation of an MRI examination alone can impact subjective and neuroendocrine stress markers, and stress acts upon the central nervous system. Therefore, scanner-related stress may influence neural activation patterns which are subject to neuroimaging studies. Especially vulnerable patient groups like anxiety patients as in the studies presented here, are likely to show enhanced responding towards the stress-evoking properties of the scanning environment. In healthy subjects though, mood seems to recover quite rapidly throughout the beginning of the scanning session, however, this might vary in clinical study populations (Muehlhan, Lueken, Wittchen, & Kirschbaum, 2011).

MRI results are easily influenced by common artifacts due to head motion or breathing (Weinberger & Radulescu, 2016). A study comparing data quality parameters between PD/AG patients and HC found patient data to be qualitatively impaired (especially concerning movement artifacts), yet effect sizes were small (Lueken et al., 2011). Enhanced movement in patients is presumably related to generally higher stress and anxiety levels, arousal and (physical) unrest. This is also likely attributable to the paradigm(s) employed. For instance, a symptom provocation paradigm in phobic patients as used in our second study expectedly leads to pronounced fear and arousal responses, most likely triggering defensive mobilization (fight or flight) or avoidance attempts, like visual avoidance by head motion to face away or closing one´s eyes. Motion artifacts should be addressed by a very thorough data quality assessment with clearly defined exclusion parameters for excessive movement and rotation as carried out in the presented studies here and/or by including movement parameters into the fMRI design model. Additional eye-tracking might be an useful tool to check for visual avoidance and task performance.

In general, neuroimaging has advanced our neurobiological knowledge and understanding of ADs, but approaches have been limited by small sample sizes, low statistical power, heterogenous imaging methodology, and low replicability (Bas-Hoogendam et al., 2020). Methodological differences in data acquisition and data analysis between studies may further contribute to inconsistent findings. Moreover, results are frequently to a substantial part

dependent on the methods used, in animals as well as in human studies (Sevenster, Visser, & D'Hooge, 2018). Varying conceptualizations also play a role when applying empirical evidence to clinical questions related to fear and anxiety. If the usage of a common and precise terminology will not be implemented into the scientific community, it will remain difficult to compare studies (Raber et al., 2019).

Publication bias constitutes a further problem across methodological approaches and fields of clinical psychology and psychotherapy research, which may lead to an overestimation of treatment effects. This may go hand in hand with questionable research practices like selective reporting of preferable results, flexibility in data analysis procedures, and "HARKing", i.e. hypothesizing after results are known (Tackett, Brandes, King, & Markon, 2019). Thus, there is a need to closely scrutinize replicability of neuroimaging findings within and across ADs, and to pay particular attention on clinical and methodological parameters accountable for heterogeneity of findings and for complicating comparability (Bas-Hoogendam et al., 2020). Thorough control and/or description of modifying factors like hardware, (pre-)processing pipelines, statistics, experimental setups, and clinical descriptions is a crucial step (Horster et al., 2020). Open data and material, pre-registration of studies (the second study presented here was for example pre-registered at ClinicalTrials.gov), registered reports, and multisite collaborations would help in augmenting replicability and in increasing the openness, transparency, and reproducibility of research (Tackett et al., 2019).

2.2. Challenges in translational research

Translational research has contributed immensely to our knowledge pool today. However, it also has its challenges. Some important differences between animal and human fear learning and threat responses are often neglected. These differences are most apparent concerning the conscious experience of fear and the human ability to voluntary use top-down cognitive strategies to modulate fear experiences (Carpenter, Pinaire, & Hofmann, 2019). The subjective feeling of fear and anxiety is, however, the leading cause why people seek treatment. The outcome of these treatments is mainly evaluated by the ability to change or reduce these subjective feelings. Approaches trying to translate findings from animal research to clinical practice often do not take this crucial fact into account, thereby restricting its validity (LeDoux & Pine, 2016). Hence, subjective emotional experience is the essence of emotion and objective manifestation as seen in behavioral and physiological states are only indicators of the inner feeling. Emotional feelings can therefore only be assessed through self-report, posing a methodological limitation to animal research. Whether animals do experience conscious emotion is, however, (still) impossible to determine. Nevertheless, behavioral and physiological

components have an important contribution to emotions and their neurobiological underpinnings, giving insight in the brain´s emotion expression and regulation (LeDoux & Hofmann, 2018). So while there are uniquely human aspects of emotions, some also reflect our ancestral past, especially on a neurobiological basis (LeDoux, 2012).

Nonetheless, it might not always be straightforward, or more complex than assumed, to draw parallels between animal and human extinction circuits on basis of neuroimaging methods. For example, the strong link between the hippocampus and contextual factors as observed in animal studies is hard to assess in humans, since the scanner environment cannot be changed easily. Contextual modulations are limited to manipulations within the presented stimulus material. Besides that, subjects cannot explore these contexts freely (Maren et al., 2013; Sevenster et al., 2018). Due to ethical boundaries and consequently, technical restrictions like spatial resolution of MRI in contrast to single-cell recordings for example, we may lack the tools to image deep brain structures or functionally heterogeneous subnuclei like in the amygdala in humans. Furthermore, whole-brain analyses in humans, as also employed in the presented studies here, reveal the involvement of brain structures which are not typically targeted in animals. This may be due to differences in animal and human conditioning paradigms, like study design (e.g. trace vs. delay conditioning), stimuli (e.g. fear relevance, ecological validity), reinforcement rate, or instruction. A closer matching of animal and human protocols, as intended in the first study of this thesis by including a separate extinction recall phase, may however aid in enhancing comparability. Thus, animal and human networks show overlap at a macroscale, but due to available techniques a comparison at the microscale remains difficult. The question is, however, if cross-species comparisons at the microscale are necessary or if identifying similarities at larger scale can already provide a sufficient learning progress (Sevenster et al., 2018).

“Human fear conditioning bridges the gap between preclinical animal research and clinical patient research” (Vervliet et al., 2013, p. 219). While mechanistic animal models are often considered too simplistic to model mental disorders, human studies are often regarded as being too descriptive and lacking mechanistic modeling. Just that, however, underlines the advantage of translational research, where animal and human sciences can complement each other in addressing the same questions at different levels, thereby mitigating the limitations of each approach alone (Milad & Quirk, 2012). Awareness of the significance of translational research is increasingly raised. Models from the laboratory setting to the patient and back again to animal models will be crucial for advancing the understanding and treatment of mental health disorders. Therefore, there is strong motivation to pursue translational procedures in mental

health research to promote indispensable innovations in therapeutic approaches (Milton & Holmes, 2018).

2.3. Alternative learning processes contributing to ADs and their treatment

Investigating emotional-associative learning processes is crucial to learn more about deficits in these processes in ADs and their relation to treatment. However, there are some aspects one has to keep in mind when interpreting (neural) findings related to extinction or exposure as solely referable to associative learning mechanisms.

Sensitization, a form of non-associative learning, is characterized by exaggerated emotional reactions to specific stimuli. The possible purpose of sensitization is to detect threats, accompanied by an increase of stimulus-specific neuronal responding. It is suggested that sensitization is supported by dysfunctional circuitry in hardwired "learning-independent" fear circuits, i.e. circuits subserving innate defensive behavior who do not require prior learning. Sensitization-associated heightened amygdala activity may therefore contribute to fear (learning) sensitization in non-experiential phobia, potentially fortified by a concomitant lack of (amygdala) habituation contributing to the persistence of this type of phobia (Garcia, 2017; Rosen, Asok, & Chakraborty, 2015). Fear sensitization might also play a role in the etiology of other ADs.

Concerning the mechanisms of action in exposure-based treatment, these mechanisms may also involve processes like habituation, which are hard to disentangle from extinction processes on a neural level (Lipka, Hoffmann, Miltner, & Straube, 2014). Habituation, also a form of non-associative learning, is characterized by reduced emotional responding to stimuli which are presented repeatedly. Its assumed function is to protect the brain from being flooded with sensory input. This is achieved by a stimulus-specific reduction of neuronal firing to repeatedly presented stimuli (Garcia, 2017). The CR decrease during extinction might be partially due to habituation processes occurring to the stimuli that control responding, since habituation diminishes the CR-evoking properties of the stimuli (McSweeney & Swindell, 2002). Exposure treatment for ADs is typically considered as CS-exposure (extinction), but might also involve US-exposure, for one challenge is, that the CS and the US are often not so clearly identifiable in clinical cases. Furthermore, fear reactions themselves can be fear-evoking and exposure eliciting fear reaction could therefore also be considered an US-exposure. The sharp distinction between CS and US starts to blur outside the laboratory and it becomes less clear which mechanism are at the basis of the fear-reducing effects of exposure treatments (Haesen & Vervliet, 2015). However, habituation during exposure is not mandatory for extinction learning to occur (Craske et al., 2008) and despite being relevant to extinction,

habituation cannot provide a complete explanation for extinction which involves presumably multiple processes (Maples-Keller & Rauch, 2020). Nevertheless, extinction and habituation processes seem to be closely intertwined and ergo hard to disentangle. This is also corroborated by evidence suggesting largely overlapping neurocircuitries underlying these neural mechanisms (Furlong, Richardson, & McNally, 2016). Consequently, it cannot be finally determined if the process of fear reduction observed throughout our VRET was attributable to extinction/inhibitory learning or habituation processes, or both. Since subjects were exposed to the feared stimulus for a prolonged time, it is likely that to some extent, habituation processes also took place.

There are several other clinically relevant cognitive-emotional factors which might be influential to the observed outcome, e.g. self-efficacy. Additionally, further processes relevant to extinction like generalization, operant avoidance, or reward learning should be kept in mind (Craske et al., 2018). Common factors like therapeutic alliance, empathy, expectations regarding treatment, cultural adaptations of evidence-based treatments, and therapist-specific effects have also been shown to influence psychotherapy outcome (Wampold, 2015). All these factors might also have contributed to the observed outcome towards the VRET. However, a standardized manual, a highly controllable environment by using VRET, and a manualized training of study therapists aimed at reducing these influences as far as possible.

3. Conclusions and outlook

3.1. Enhancing extinction learning

Extinction represents a key mechanism underlying exposure treatment in ADs. Therefore, maximizing extinction learning and ergo, the efficacy of exposure treatment, is of high interest. Especially the enhancement of the long-term effects of fear extinction poses a tough challenge for (pre-)clinical anxiety research (Haesen & Vervliet, 2015). There exist various strategies targeting the enhancement of extinction on different levels, like procedural, behavioral, pharmacological, or neuromodulatory approaches. The identification of moderators of extinction learning and its recall, or respectively, treatment response, could aid in stratifying patients and personalizing therapy by selecting adequate treatment options and/or extinction enhancement strategies.

Two prevailing types of enhancement strategies are procedural enhancement and flanking enhancement. Procedural enhancement strategies mainly focus on a maximized violation of dysfunctional expectancies (prediction error) and on diminishing context- and stimulus-dependent specificity of extinction learning. They also include the removal of safety

signals, safety behaviors, and methods like affect labeling. Flanking strategies focus on the general enhancement of learning, memory (re-)consolidation, and memory retrieval by preparing and post-processing of the exposure. They include for example physical exercise or positive mood induction prior to exposure or retrieval cues for better memory accessibility (Pittig et al., 2016). These techniques have mainly been applied in laboratory settings or with clinical analogue samples, allowing only limited inferences about their efficacy in naturalistic exposure treatment. Moreover, individual differences in responding to these strategies are also not clear, yet. Future research should address the question, which boosting strategies are the most beneficial for whom (Pittig, Treanor, LeBeau, & Craske, 2018). However, behavioral strategies to enhance extinction may represent a potent tool for the clinical practice to further improve the efficacy of exposure treatments (Pittig et al., 2016).

The advancing understanding of the critical involvement of specific brain regions in mental disorders and their therapy has sparked great interest in neurophysiology-based therapeutic interventions which can directly interact with dysfunctional brain regions and related circuitry (Bajbouj & Padberg, 2014). Neurostimulatory and neuromodulatory treatments bear potential as neuroscience-informed treatment strategies since they may provide access to basic emotional-associative learning processes and memory circuitries (Ressler & Mayberg, 2007) and could be useful tools for augmenting fear extinction. By applying these methods, the neural nodes of fear extinction could be targeted to diminish behavioral deficits that may subsequently translate into clinical improvement (Marin et al., 2014). For example, in a study in SP using high-frequency repetitive transcranial magnetic stimulation (rTMS) over the vmPFC during VRET improved treatment efficacy compared to sham stimulation. rTMS might ergo be useful as therapeutic add-on for exposure-based therapies (Herrmann et al., 2017). Similarly, using transcranial direct current stimulation (tDCS) over the vmPFC in healthy subjects also enhanced fear extinction in comparison to a sham stimulation. tDCS over the vmPFC appeared to diminish the sympathetic component of fear reactions during extinction. Results also suggested that prolonged tDCS facilitated extinction consolidation (Vicario et al., 2020). Non-invasive transcutaneous vagus nerve stimulation (tVNS) during extinction training in a healthy sample also showed promising results, since it facilitated the inhibition of fear potentiated startle responses and cognitive risk assessments. This again promoted the formation, consolidation, and long-term recall of the extinction memory and thereby prevention of the ROF (Szeska, Richter, Wendt, Weymar, & Hamm, 2020).

Regarding pharmacological approaches, D-Cycloserine (DCS), a *N*-methyl-D-aspartate (NMDA) partial agonist, has been shown to enhance extinction learning in rodents and humans.

NMDA receptors can be found, inter alia, in brain regions related to fear processing and fear learning like the amygdala and the hippocampus (Davis, Ressler, Rothbaum, & Richardson, 2006). DCS augments exposure-based therapy by speeding up extinction via compounds that impact neuroplasticity (Norberg, Krystal, & Tolin, 2008). Some studies suggest that DCS may rather accelerate extinction (Chasson et al., 2010) than improve the overall outcome. Due to strongly varying findings from null-results to considerable effects, results remain inconclusive. Nevertheless, a recent study in healthy subjects by Ebrahimi et al.(2020) found DCS (compared to a placebo group) to facilitate long-term retention of extinction, which was accompanied by a downregulation of amygdala activation from extinction training to extinction recall. This was interpreted as a prevention of the ROF due to DCS. Deeper knowledge on the mechanisms of DCS during experimental assessment of extinction learning and recall could aid in identifying potential moderators of its augmentation effect in patient populations. These insights may be useful for stratifying patients and personalizing treatments (Ebrahimi et al., 2020). Further research is required to establish guidelines concerning dosage, timing of administration, contraindications, and implementation of DCS. Notwithstanding, DCS may be helpful in speeding up the effects of exposure treatment, especially for those with severe anxiety and for those, who did not benefit from exposure treatment in the past (La Buissonnière-Ariza, Schneider, & Storch, 2019). Thus, DCS might be useful in clinical populations for making exposure treatments more efficacious, hence decreasing non-adherence, dropouts, and relapse rates. In the long run, it would be ideal to use these promising methods combined with exposure therapy to promote the formation of a strong memory trace during extinction which would reduce the risk of relapse. Future studies are however needed as a proof of this hypothesis.

Despite compelling evidence, future research still needs to assess whether individual differences in extinction and extinction recall clearly have predictive value for the outcome of exposure treatment, since this question has hardly been addressed systematically (Scheveneels et al., 2016). However, studies emerging on this topic are rather encouraging. In a treatment analogue study in spider fearful participants, an enhanced extinction learning capacity correlated with better outcomes (Forcadell et al., 2017). Better extinction learning indicated by behavioral ratings and neural activation patterns was associated with a greater symptom reduction following exposure in public speaking anxiety (Ball, Knapp, Paulus, & Stein, 2017). In spider phobia, fear extinction retrieval was linked to the ability to complete exposure in a predetermined time and to exposure therapy outcome (Raeder, Merz, Margraf, & Zlomuzica, 2020), whereas in another study neural activation during extinction learning was predictive of exposure therapy outcome, while extinction recall had no predictive value (Lange et al., 2020).

However, there are already endeavors by creating laboratory extinction learning paradigms which are methodological well-matched to those extinction learning processes activated during exposure treatment (Hollandt et al., 2020). Further clinical translation studies are necessary to validate basic research strategies directed at treatment optimization (Pittig et al., 2018).

Of note, the success of novel treatment approaches or enhancement strategies will be further strengthened by grounding them in a substantial body of knowledge of their mechanisms of action at the neural level. Ideally, these approaches can be attuned to the normalization of neurobiological deviations like aberrant activation patterns within relevant brain circuits (Singewald & Holmes, 2019).

3.2. Personalizing treatments via machine learning frameworks

In the last 25 years, the field of neuroimaging research on ADs has significantly shifted from the mere characterization of pathophysiology to the description of how psychotherapy can change the brain (Messina, Sambin, Palmieri, & Viviani, 2013). So far, progresses in understanding the brain have not been reflected in ameliorated clinical outcomes, since most contemporary therapy approaches emerged decades ago (LeDoux & Pine, 2016). Despite initial results in neuroimaging, the application of results to clinical practice is insufficient, as they do not translate into meaningful information for the individual patient (Walter et al., 2019; Woo, Chang, Lindquist, & Wager, 2017).

Recently, the inference statistical approach, which is applied to find differences in efficacy between groups or mechanisms of several interventions, has been complemented by machine learning approaches. Machine learning methods enable the use of a set of multimodal predictors (e.g. genetics, neuroimaging, clinical data), for (several) outcome variables (e.g. behavior, clinical characteristics), avoiding the need of multiple comparisons and making the detection of subtle variations, e.g. in the brain, possible (Bzdok & Meyer-Lindenberg, 2018; Orrù, Pettersson-Yeo, Marquand, Sartori, & Mechelli, 2012; Woo et al., 2017). Machine learning includes hypothesis-free methods which is beneficial for examining complex data sets (Valletta, Torney, Kings, Thornton, & Madden, 2017).

Multivariate pattern recognition embedded within a machine learning framework is a technology that has strongly influenced medical research (Darcy, Louie, & Roberts, 2016) and that also bears potential for the field of mental health research and patient care (Orrù et al., 2012; Woo et al., 2017). By means of machine learning an individual patient prediction of treatment (non-)response is made possible (Lueken & Hahn, 2016) and can inform about personalized treatment selection, the need of augmentation with other techniques or the treatment dose, to help in sparing ineffective treatments, associated side effects on patient

compliance, disease chronification or aggravation, and direct and indirect costs. However, despite their high prevalence, ADs are strongly underrepresented in predictive modeling (2.5% from all neuropsychiatric conditions) and predictive modeling accounts are still dominated by mere cross-sectional classification analyses (case/control distinction). Longitudinal data on theranostic markers (i.e. markers that predict treatment outcome) (Woo et al., 2017), as well as cross-site validations, are still largely missing.

Previous research characterizing the mechanisms of action underlying exposure and patient features associated with treatment outcome is dominated by approaches focusing on the group-level. This mechanistic approach aimed at optimizing models of disease and treatments targeting at disorder-specific brain circuits (Lueken & Hahn, 2016). One major shortcoming of this group-level approach is the lack of individual or patient-specific prediction. The already mentioned rather unsatisfying response rates and effect sizes (Gloster et al., 2011; Huhn et al., 2014; Loerinc et al., 2015; Taylor et al., 2012) warrant researchers to focus more strongly on novel methods that are able to generate single patient predictions and thus may guide more personalized treatment approaches. Of note, a number of neuroimaging studies on different forms of ADs (Ball, Stein, Ramsawh, Campbell-Sills, & Paulus, 2014; Hahn et al., 2015; Månsson et al., 2015; Sundermann et al., 2017) that used machine learning methods to generate predictions of treatment outcome on the single case level achieved prediction accuracies ranging from 46 % - 92 %.

Since traditional disease categories are increasingly questioned to represent underlying neurobiological classes (Hyman, 2007), machine learning seems to be an appropriate tool enabling the detection of complex patterns in brain, behavior, and genes. There is evidence suggesting that data-derived subgroups within specific patient groups are better suited to predict treatment outcome than DSM or ICD diagnoses which include heterogeneous endophenotypes (Hahn, Nierenberg, & Whitfield-Gabrieli, 2017). There are as well several important methodological benefits of multivariate predictive models (Woo et al., 2017). First of all, the direction of inference is reversed, i.e. brain features, (epi-)genetic and clinical characteristics serve as a set of predictors and treatment response as an outcome. Second, the problem of multiple testing can be overcome by the integration of existing data into one model. And lastly, the prognostic value is assessed by evaluating the performance of the model in an independent sample and thereby yielding valid estimates of effect size and ergo clinical significance (Woo et al., 2017). The applied combination of multiple units of analysis, e.g. (epi-)genetic, neural systems and clinical readouts can be adequately processed via machine

learning methods. By means of several units of analysis, the optimal (cost-efficient) predictors become identifiable.

3.3. The age of RDoC

Contemporary categorical diagnostic systems for mental disorders build on presenting signs and symptoms, not integrating relevant neurobiological and behavioral systems and thereby limiting research on etiology, pathophysiology, and the development of novel treatments. Since DSM and ICD disease categories do not map well onto genetic, neuroscientific, and behavioral research results, the validity of the disease entities has been put up for debate. This makes it difficult to translate research from basic animal or human studies to a systematic understanding of pathology and its treatment. The NIMH project RDoC (Research Domain Criteria) aims at establishing a research classification system for mental disorders based upon fundamental biobehavioral systems. In this dimensional approach, basic science from various research fields serves as starting point and disorders are rated as disruptions of the normal-range operation of these systems, with focus on the mechanisms leading to dysfunctions of varying degrees (Cuthbert & Insel, 2013). RDoC tries to reconceptualize mental disorders into transdiagnostic functional dimensional constructs on the basis of neurobiological measures and observable behavior. By understanding the neurobiological underpinnings and pathophysiology of the relevant processes, biomarker development can be advanced for disease prediction and treatment response (Kelly, Clarke, Cryan, & Dinan, 2018).

The RDoC matrix consists of six major domains of human functioning: negative valence systems, positive valence systems, cognitive systems, systems for social processes, arousal and regulatory systems, and sensorimotor systems. These domains contain several (sub-)constructs which are studied along a continuum of functioning. For the measurements of constructs, different units of analysis are available: genes, molecules, cells, circuits, physiology, behavior, self-report, and according paradigms. The RDoC matrix is designed to evolve due to new research results and thus will be modified to integrate new and/or revised domains and/or constructs (for further details see https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/about-rdoc.shtml).

“RDoC-ian” research is still in its infancy (Lonsdorf & Richter, 2017), but there are endeavors to conduct studies using RDoC-ian principles, like integrating various biobehavioral measures and analyzing constructs dimensionally instead of categorically. Fear conditioning is ascribed to the RDoC domain of negative valence systems, and more precisely to the construct of acute threat. As an example of RDoC-ian research, a fear conditioning paradigm in AD patients using a transdiagnostic dimensional approach, could show that individuals with a

higher UCR during conditioning, i.e. acute threat learning, showed a deficient extinction recall, i.e. higher threat responses during recall, the next day. This suggests that the immediate response to the US, which correlates with a higher activation of fear circuitry and higher arousal, has predictive value of extinction recall irrespective of the diagnosis. Threat-related arousal might therefore be a useful tool to identify subjects at greater risk of relapse after therapy (Marin, Hammoud, Klumpp, Simon, & Milad, 2020; Marin & Milad, 2020).

Fear conditioning is one of the most prominent paradigms of behavioral neuroscience for investigating the fundamentals of learning and memory, the neurobiology of emotion, and as a model for the pathogenesis of ADs (Beckers et al., 2013). Surprisingly, allocating fear conditioning into the RDoC matrix is not unequivocal, though. It is listed as a paradigm for investigating acute threat. However, fear conditioning and fear extinction are also different yet related general learning processes. While conditioning creates an excitatory memory trace, extinction results in an inhibitory memory trace. Therefore, it also fits into the cognitive system domain. Fear conditioning as an umbrella term (i.e., fear acquisition, extinction, extinction recall, ROF) cannot be reduced to a single RDoC domain, but rather fulfills itself the central criteria to qualify as an RDoC construct, not only an operationalization thereof (Lonsdorf & Richter, 2017). Moreover, extinction and extinction recall are assumed essential to exposure therapy and its long-term success (Scheveneels et al., 2016) and further underline the importance of these processes beyond being a paradigm for assessing acute threat.

It has also been proposed to include emotion regulation as an additional RDoC domain, since it plays a crucial role in many mental disorders and might therefore represent a key transdiagnostic factor within RDoC as an organizing framework. It is, however, also relevant to normal functioning. Emotion regulation describes a unique affective regulatory process which may be best conceptualized as a new domain. It constitutes a functional consequence of dynamic interaction patterns among the other domains and is therefore not reducible to the existing domains. Emotion regulation can be empirically grounded across all units of analyses like circuits, physiology or behavior (K. C. Fernandez, Jazaieri, & Gross, 2016). Furthermore, since emotion (dys-)regulation is assumed an transdiagnostic construct central to the development and maintenance of psychopathology, changes in emotion regulation deficits should occur after successful treatment (Sloan et al., 2017).

So, while RDoC may represent a promising starting point in delineating underlying transdiagnostic aspects of mental disorders on a dimensional neurobiobehavioral level, there still seems to be a shortage of the integration of neurofunctional systems/constructs/units relevant to the therapy of these disorders. From a clinical point of view, RDoC needs to integrate

more strongly the mechanisms of action relevant to therapy, like for example extinction processes. Emotion regulation as a key concept of psychopathology and treatment encompasses complex processes that span across all domains, which is indicative that ideally, it may be implemented as an additional domain. Our results (figure 15) also span various RDoC domains, however, unequivocally allocating essential elements like emotion regulation capacities remains difficult, the same applies to extinction, and extinction recall.

At the present time, RDoC focuses on "understanding the nature of mental health and illness in terms of varying degrees of dysfunction in general psychological/biological systems" (retrieved from https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/about-rdoc.shtml), but it does not sufficiently integrate therapy and related processes, yet. From a clinical perspective, it would be of great importance to further establish a treatment RDoC domain, integrating neurobiobehavioral treatment-relevant mechanisms of action and moderators of treatment (non-)response. RDoC could also be useful to identify neuroscience-based predictors of treatment response by systematically integrating various kinds of data into treatment matching paradigms (Hershenberg & Goldfried, 2015).

Taken together, RDoC represents a seminal research framework for investigating mental disorders. However, the framework itself and researchers using it would presumably benefit from establishing additional domains for central multi-faceted core concepts like fear conditioning and extinction, emotion regulation, and treatment-related variables which are still hard to allocate unequivocally within the present framework since they span across multiple domains. In the long run, the identification and elaboration of transdiagnostic constructs could create an etiologically-based nosology which might promote the clinical use of dimensional measurements, and by doing so ameliorating prevention, diagnosis, and treatment of psychopathology (Sharp, Miller, & Heller, 2015).

3.4. Concluding remarks

Through progress in both basic and clinical research, fear conditioning and extinction turned out to be enlightening and viable translational models for understanding and treating ADs (Craske et al., 2018). The current thesis strived for translating findings from very basic emotional-associative learning mechanisms in PD into the clinical practice of behavioral exposure in SP. Indeed, we observed aberrations in emotional-associative learning processes in PD patients compared to HC indicated by an accelerated fear acquisition and an attenuated extinction recall. Furthermore, pre-treatment differences related to defensive, regulatory, attentional, and perceptual processes may exert a moderating influence on treatment outcome to behavioral exposure in spider phobia. Although our results clearly need further replication,

on an integrative meta level, our results point to a hyperactive defensive network system and deficient emotion regulation processes (including extinction processes), and top-down control in ADs. This speaks in favor of transdiagnostic deficits in important functional domains in ADs, as conceptualized by the RDoC framework. Nevertheless, the RDoC framework would provide an even better starting point by establishing additional separate domains for key concepts like fear conditioning and extinction, emotion regulation, treatment-related mechanisms of action, and moderators of treatment outcome. This could establish a neurobiobehavioral scaffolding for research targeting these deficits in overarching domains like emotion regulation processes, for example by augmenting extinction learning or by means of promising tools like NF, with the aim of improving treatment outcomes.

A remaining major challenge for research is still posed by the awareness that treatment response varies strongly in individuals and that there is a considerable treatment gap for ADs. Understanding why a treatment has failed is as important and informative as why it has worked, and obtaining more efficacious treatments might therefore necessitate a refinement of contemporary approaches, innovation to develop novel ones, or personalization by patient-tailored treatments (Goodwin et al., 2018). Research should also focus strongly on the commonalities and differences in treatment response signatures across disorders and patients, and on the question if there´s an overarching signature of treatment (non-)response. Evidence further suggests that treatments would be well-advised to put a stronger focus on the long-term retrieval of extinction, since successful reductions of fear are often short-lived and followed by a ROF (Vervliet et al., 2013). The remaining risk of relapse represents a major constraint of current treatment approaches (Singewald & Holmes, 2019). Thus, a critical challenge is not only to achieve a fear reduction, but to uphold it in the course of time to prevent relapse (Vervliet et al., 2013). The problems of treatment non-response, the ROF, and full relapse still need to be addressed intensely by future research (Craske et al., 2018).

The detection of pre-treatment moderators of clinical response, for instance via machine learning frameworks, may help in supporting clinical decision making on individually tailored treatment approaches or respectively, to avoid ineffective treatment and its related financial costs. In the long run, the identification of neurobiological markers which are capable of detecting non-responders a priori represents an ultimate goal. On the other hand, learning which neural mechanisms underly effective treatment approaches and which markers characterize treatment non-responders may help in developing alternative treatment options (Lueken & Hahn, 2016).

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LIST OF ABBREVIATIONS

A1 = early acquisition
A2 = late acquisition
AAL = automatic anatomical labeling
ABM = attention bias modification training
ACC = anterior cingulate cortex
AC-PC = anterior commissure – posterior commissure
ACQ = Agoraphobic Cognitions Questionnaire
AD(s) = anxiety disorder(s)
ADS-K = Allgemeine Depressions-Skala
ANOVA = Analysis of Variance
AS = Angststörung(en)
ASI = Anxiety Sensitivity Index
BAI = Beck Anxiety Inventory
BAT = Behavioral Avoidance Test
BDI = Beck Depression Inventory
BDI-II = Beck Depression Inventory II
B-I-I = blood-injection-injury
BIS-BAS = Behavioral Inhibition System – Behavioral Activation System
BLA = basolateral amygdala
BMBF = Bundesministerium für Bildung und Forschung (Federal Ministry of Education and Research)
BOLD = blood-oxygen-level-dependent
BSSS = Berliner Social Support Skalen
CBT = cognitive-behavioral therapy
CEA = central amygdala
CERQ = Cognitive Emotion Regulation Questionnaire
CGI = Clinical Global Impressions Scale
CR = conditioned response
CRC = Collaborative Research Center
CS = conditioned stimulus
CS- = CS never paired with the US
CS+ = CS paired with the US
CSF = cerebrospinal fluid
CTQ = Childhood Trauma Questionnaire
dACC = dorsal anterior cingulate cortex
DARTEL = Diffeomorphic Anatomical Registration using Exponentiated Lie algebra
DCM = dynamic causal modelling
DCS = D-Cycloserine
DFG = Deutsche Forschungsgemeinschaft (German Research Foundation)
dlPFC = dorsolateral prefrontal cortex
dmPFC = dorsomedial prefrontal cortex
DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders IV, text revision
EDA = electrodermal activity
EoI = effect of interest
EPI = echo-planar imaging
ER1 = return of fear
ER2 = early extinction recall
ER3 = late extinction recall
ET1 = recall of CR
ET2 = early extinction training
ET3 = late extinction training
FAS = Fragebogen zur Angst vor Spinnen
FEAS = Fragebogen zu Ekel und Angst vor Spinnen
FFA = fusiform face area
FIR = first interval response
fMRI = functional magnetic resonance imaging
FOV = field of view
FU = follow-up
FWE = familywise error
FWHM = full-width at half-maximum
GAD = generalized anxiety disorder
GLM = general linear model
GM = grey matter
GMV = grey matter volume
GSE = General Self Efficacy Scale
H = habituation phase
HC = healthy controls
HMD = head-mounted display
HRF = hemodynamic response function
ICD = International Statistical Classification of Diseases and Related Health Problems
IFG = inferior frontal gyrus

IFO = inferior frontal operculum
IL = infralimbic cortex
IOG = inferior occipital gyrus
IPQ = Igroup Presence Questionnaire
ITC = intercalated cell masses
ITG = inferior temporal gyrus
k_E = cluster extent threshold
KFB = Kurzer Fragebogen zu Belastungen
LSAS = Liebowitz Social Anxiety Scale
LTE = List of threatening Experiences
M = mean
MDD = major depressive disorder
Mdn = median
MFG = middle frontal gyrus
MNI = Montreal Neurologic Institute
MOG = middle occipital gyrus
mPFC = medial prefrontal cortex
MPRAGE = magnetization prepared rapid gradient echo
MRI = magnetic resonance imaging
MTG = middle temporal gyrus
NF = neurofeedback
NIMH = National Institute of Mental Health
NMDA = *N*-methyl-D-aspartate
OCD = obsessive-compulsive disorder
OFC = orbitofrontal cortex
PAG = periaqueductal grey
PANAS = Positive and Negative Affect Schedule
PAS = Panic and Agoraphobia Scale
PCC = posterior cingulate cortex
PD = panic disorder
PD/AG = panic disorder with agoraphobia
PFC = prefrontal cortex
PL = prelimbic cortex
PPI = psychophysiological interaction
PSWQ = Penn State Worry Questionnaire
PTSD = posttraumatic stress disorder
QOL = quality of life
RCT = randomized controlled trial
RDoC = Research Domain Criteria
ROF = return of fear
ROI = region of interest
rTMS = repetitive transcranial magnetic stimulation
SAD = social anxiety disorder
SCID = Structured Clinical Interview
SCR = skin conductance response
SD = standard deviation
SDS-CM = Social Desirability Scale
SEM = standard error of the mean
SFG = superior frontal gyrus
SIGH-A = Structured Interview Guide for the Hamilton Anxiety Scale
SMA = supplementary motor area
SOG = superior occipital gyrus
SP = specific phobia
SPAI = Social Phobia and Anxiety Inventory
SPF = sustained and phasic fear paradigm
SPQ = spider phobia questionnaire
SS-A = Social Support Appraisals Scale
STAI = State-Trait Anxiety Inventory
STG = superior temporal gyrus
SVC = small volume correction
SVF = Stressverarbeitungsfragebogen
tDCS = transcranial direct current stimulation
TE = echo time
TEMPS-A = Temperamentskala
TIV = total intracranial volume
TR = repetition time
tVNS = transcutaneous vagus nerve stimulation
UCR = unconditioned reaction
UI-18 = Intolerance of Uncertainty Scale
US = unconditioned stimulus
vlPFC = ventrolateral prefrontal cortex
vmPFC = ventromedial prefrontal cortex
VOI = volume of interest
VR = virtual reality
VRET = exposure-based treatment in Virtual Reality
WM = white matter

LIST OF FIGURES

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APPENDIX

1. Permission for reuse

2. Supplemental material and results: Characterizing the nature of emotional-associative learning deficits in panic disorder

2.1. Contingency Awareness

After the entire conditioning procedure, contingency awareness was assessed by a short questionnaire on day 3. Participants were asked how often and when the scream was presented, how many different faces they saw in general, and how many different faces were presented prior to the scream. They were also asked to describe the face(s) directly before the scream appeared and to tick the face that was followed by the scream or the option that there was no systematization. Among all participants, 20% showed no contingency awareness, while 80% in total were aware which stimulus was followed by a panic scream. There were 10% unaware HC and 30% of unaware patients, however, this difference in contingency awareness between patients and HC was not significant (χ^2 (1) = 1.250, p = 0.264).

3. Supplemental material and results: Characterizing moderators of treatment response towards behavioral exposure in spider phobia

3.1. Overview of all assessments

Table S1. Overview of assessments in chronological order arranged according to the type of measurement.

Assessment	Baseline	MRI	VRET	Post-treatment	Follow-up
Clinical					
SCID	**X**				**X**
CGI	**X**			**X**	**X**
SPQ	**X**			**X**	**X**
Behavioral					
BAT	**X**			**X**	**X**
Neurobiological					
blood sampling	**X**			**X**	**X**
EDA	**X**			**X**	**X**
(f)MRI		**X**			
Psychometric					
Igroup Presence Questionnaire (IPQ)			**X**		
Anxiety Sensitivity Index (ASI)	**X**			**X**	**X**
Beck Depression Inventory II (BDI-II)	**X**			**X**	**X**
General Self-Efficacy Scale (GSE)	**X**			**X**	**X**
PROMIS Scales for DSM-5 (anxiety)	**X**			**X**	**X**
State-Trait Anxiety Inventory (STAI-Trait)	**X**			**X**	**X**
Intolerance of Uncertainty Scale (UI-18)	**X**			**X**	**X**
Beck Anxiety Inventory (BAI)	**X**				
List of threatening Experiences (LTE)	**X**				
Liebowitz Social Anxiety Scale (LSAS)	**X**				
Allgemeine Depressions-Skala (ADS-K)[1]	**X**				
Agoraphobic Cognitions Questionnaire (ACQ)	**X**				
Penn State Worry Questionnaire (PSWQ)	**X**				
Social Phobia and Anxiety Inventory (SPAI)	**X**				
Positive and Negative Affect Schedule (PANAS-Trait)	**X**				
Childhood Trauma Questionnaire (CTQ)	**X**				
Life Calendar	**X**				
Kurzer Fragebogen zu Belastungen (KFB)[2]	**X**				

Table S1 (continued).

Brief COPE	**X**				
Fragebogen zur Angst vor Spinnen (FAS)[3]	**X**				
Fragebogen Ekel und Angst vor Spinnen (FEAS)[4]	**X**				
Behavioral Inhibition System – Behavioral Activation System (BIS-BAS)				**X**	
Trier Inventory for Chronic Stress (TICS)				**X**	
Stressverarbeitungsfragebogen (SVF-78)[5]				**X**	
Cognitive Emotion Regulation Questionnaire (CERQ)				**X**	
Social Desirability Scale (SDS-CM)				**X**	
Temperamentskala (TEMPS-A)[6]				**X**	
Social Support Appraisals Scale (SS-A)				**X**	
Berliner Social Support Skalen (BSSS)[7]				**X**	

[1] German version of the Center for Epidemiological Studies Depression Scale (CES-D-scale, NIMH)
[2] "Brief questionnaire about stresses and strains"
[3] German version of Fear of Spiders Questionnaire (FSQ, Szymanski & O'Donohue, 1995)
[4] "Questionnaire on Disgust and Fear of Spiders"
[5] "Coping with Stress Inventory"
[6] German version of the "Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire"
[7] "Berlin Social Support Scales"

SCID: Structured clinical interview for DSM-IV; CGI: Clinical Global Impression Scale; SPQ: Spider Phobia Questionnaire; BAT: Behavioral Avoidance Test; EDA: electrodermal activity; (f)MRI: (functional) magnetic resonance imaging.

IPQ (Schubert, 2003), **ASI** (Reiss et al., 1986), **BDI-II** (Kühner, Bürger, Keller, & Hautzinger, 2007), **GSE** (Jerusalem & Schwarzer, 1993), **PROMIS** (Wahl, Löwe, & Rose, 2011), **STAI** (Laux, 1981), **UI-18** (Gerlach, Andor, & Patzelt, 2008), **BAI** (Margraf & Ehlers, 2007), **LTE** (Brugha & Cragg, 1990), **LSAS** (Heimberg et al., 1999), **ADS** (Hautzinger & Bailer, 1993), **ACQ** (Chambless, Caputo, Bright, & Gallagher, 1984), **PSWQ** (van Rijsoort, Emmelkamp, & Vervaeke, 1999), **SPAI** (Turner, Beidel, Dancu, & Stanley, 1989), **PANAS** (Watson, Clark, & Tellegen, 1988), **CTQ** (Wingenfeld et al., 2010), **Life calendar** (Canli et al., 2006), **KFB** (Flor, 1991), **COPE** (Knoll, Rieckmann, & Schwarzer, 2005), **FAS** (Rinck et al., 2002), **FEAS** (Schaller, Gerdes, & Alpers, 2006), **BIS-BAS** (Strobel, Beauducel, & Debener, 2001), **TICS** (Schulz, 2008), **SVF-78** (Jahnke, Erdmann, & Kallus, 2002), **CERQ** (Loch, Hiller, & Witthöft, 2011), **SDS-CM** (Luck & Timaeus, 1969), **TEMPS-A** (Akiskal, Brieger, Mundt, Angst, & Marneros, 2002), **SS-A** (Vaux et al., 1986), **BSSS** (Schwarzer & Schulz, 2003).

3.2. Additional sample characteristics tables

Table S2. Sample characteristics for the SPF-sample grouped by the secondary outcome criterion BAT (N = 81).

	responders n = 42 (51.58%)	non-responders n = 39 (48.15%)	χ^2 or *t* (df)	*p*
Demographic characteristics				
Age (years)	28.71 (9.25)	28.56 (8.53)	0.08 (79)	0.940
Female gender [n (%)]	34 (80.95)	36 (92.31)	2.22 (1)	0.136
Years of education	14.21 (3.47)	14.64 (3.15)	-0.58 (79)	0.565
Clinical and psychometric characteristics				
SPQ sum score	23.31 (2.58)	22.92 (2.28)	0.71 (79)	0.478
BAT final distance (cm)	163.01 (70.57)	175.65 (50.53)	-0.93 (74.33)	0.354
Duration exposure session (min)	81.12 (24.38)	91.00 (26.77)	-1.74 (79)	0.086
Within-session extinction	46.80 (19.29)	44.39 (19.02)	0.57 (79)	0.573
Age of onset	8.70 (4.54)[a]	7.33 (3.00)	1.58 (67.87)	0.118
Comorbidity [n (%)]	0 (0.00)	2 (5.13)	2.21 (1)	0.137
major depression	0 (0.00)	2 (5.13)		
subordinate animal phobia	0 (0.00)	0 (0.00)		
CGI [n (%)]			2.77 (3)	0.429
Mildly ill	9 (21.43)	6 (15.38)		
Moderately ill	13 (30.95)	18 (46.15)		
Markedly ill	19 (45.24)	15 (38.46)		
Severely ill	1 (2.38)	0 (0)		
FEAS anxiety	102.44 (12.81)[b]	100.59 (15.52)	0.58 (78)	0.562
FEAS disgust	109.41 (12.77)[c]	110.74 (11.50)	-0.49 (78)	0.627
STAI- Trait	36.10 (10.08)	36.33 (8.27)	-0.12 (79)	0.908
BDI-II total	3.07 (3.82)	3.54 (4.70)	-0.49 (79)	0.624
ASI-3	15.36 (10.16)	14.95 (9.91)	0.18 (79)	0.855
GSE	2.30 (0.43)	2.88 (0.42)	1.24 (79)	0.220

SPQ: Spider Phobia Questionnaire; BAT: Behavioral Avoidance Test; CGI: Clinical Global Impression; FEAS: Fragebogen zu Ekel und Angst vor Spinnen (questionnaire regarding disgust and fear of spiders); STAI: State Trait Anxiety Inventory; BDI-II: Beck Depression Inventory II; ASI-3: Anxiety Sensitivity Index; GSE: General Self Efficacy Scale.

[a] available for n = 40; [b] available for n = 41; [c] available for n = 41. Values given as mean (standard deviation) except where noted.

Table S3. Sample characteristics for the SPF-sample grouped by the magnitude of the within-session extinction (N = 81).

	high n = 40 (49.38%)	low n = 41 (50.62%)	χ^2 or *t* (df)	*p*
Demographic characteristics				
Age (years)	26.30 (5.64)	30.93 (10.72)	2.44 (60.91)	<0.05
Female gender [n (%)]	35 (87.50)	35 (85.37)	0.08 (1)	0.779
Years of education	14.95 (2.98)	13.90 (3.56)	-1.44 (77.25)	0.154
Clinical and psychometric characteristics				
SPQ sum score	23.20 (2.79)	23.05 (2.05)	-0.28 (71.48)	0.782
BAT final distance (cm)	163.96 (66.65)	174.11 (56.82)	0.74 (79)	0.463
Duration exposure session (min)	83.43 (27.60)	88.27 (24.18)	-0.84 (79)	0.403
Within-session extinction	61.03 (11.01)	30.62 (11.91)	11.92 (79)	<0.001
Age of onset	8.85 (4.05)[a]	7.23 (3.61)[b]	-1.88 (77)	0.064
Comorbidity [n (%)]	2 (5.00)	0 (0.00)	2.10 (1)	0.147
major depression	2 (5.00)	0 (0.00)		
subordinate animal phobia	0 (0.00)	0 (0.00)		
CGI [n (%)]			1.20 (3)	0.752
Mildly ill	8 (20.00)	7 (17.07)		
Moderately ill	15 (37.50)	16 (39.02)		
Markedly ill	16 (40.00)	18 (43.90)		
Severely ill	1 (2.50)	0 (0.00)		
FEAS anxiety	102.56 (11.93)[c]	100.56 (16.05)	0.63 (78)	0.530
FEAS disgust	110.72 (13.63)[d]	109.44 (10.60)	0.47 (78)	0.640
STAI- Trait	35.53 (10.04)	36.88 (8.37)	-0.66 (79)	0.511
BDI-II total	3.05 (4.22)	3.54 (4.30)	-0.51 (79)	0.609
ASI-3	15.50 (9.54)	14.83 (10.50)	0.30 (79)	0.764
GSE	2.98 (0.44)	2.90 (0.42)	0.81 (79)	0.421

SPQ: Spider Phobia Questionnaire; BAT: Behavioral Avoidance Test; CGI: Clinical Global Impression; FEAS: Fragebogen zu Ekel und Angst vor Spinnen (questionnaire regarding disgust and fear of spiders); STAI: State Trait Anxiety Inventory; BDI-II: Beck Depression Inventory II; ASI-3: Anxiety Sensitivity Index; GSE: General Self Efficacy Scale.

[a] available for n = 39; [b] available for n = 40; [c] available for n = 39; [d] available for n = 39. Values given as mean (standard deviation) except where noted.

Table S4. Sample characteristics for the morphometry sample grouped by the secondary outcome criterion BAT (N = 87).

	responders n = 45 (51.72%)	non-responders n = 42 (48.28%)	χ^2 or *t* (df)	*p*
Demographic characteristics				
Age (years)	29.69 (9.70)	29.07 (9.65)	0.30 (85)	0.767
Female gender [n (%)]	36 (80.00)	39 (92.86)	3.02 (1)	0.082
Years of education	13.91 (3.54)	14.79 (3.09)	-1.23 (84.63)	0.222
Clinical and psychometric characteristics				
SPQ sum score	23.27 (2.50)	22.90 (2.21)	0.71 (85)	0.477
BAT final distance (cm)	166.74 (71.74)	177.55 (50.47)	-0.82 (79.15)	0.417
Duration exposure session (min)	81.27 (24.14)	92.12 (26.67)	-1.99 (85)	0.050
Within-session extinction	48.28 (19.59)	43.53 (19.00)	1.15 (85)	0.254
Age of onset	9.05 (4.64)[a]	7.38 (3.19)	1.93 (74.63)	0.057
Comorbidity [n (%)]	0 (0.00)	3 (7.14)	3.33 (2)	0.068
major depression	0 (0.00)	2 (4.76)		
subordinate animal phobia	0 (0.00)	1 (2.38)		
CGI [n (%)]			2.63 (3)	0.452
Mildly ill	9 (20.00)	6 (14.29)		
Moderately ill	13 (28.89)	19 (45.24)		
Markedly ill	21 (46.67)	16 (38.10)		
Severely ill	2 (4.44)	1 (2.38)		
FEAS anxiety	102.45 (12.84)[b]	100.69 (15.50)	0.58 (84)	0.566
FEAS disgust	109.86 (12.55)[c]	110.67 (11.40)	-0.31 (84)	0.757
STAI- Trait	36.29 (9.91)	36.29 (8.03)	0.002 (85)	0.999
BDI-II total	3.40 (3.93)	3.64 (4.58)	-0.27 (85)	0.791
ASI-3	15.64 (9.95)	15.48 (10.06)	0.08 (85)	0.938
GSE	2.99 (0.42)	2.89 (0.41)	1.13 (85)	0.261

SPQ: Spider Phobia Questionnaire; BAT: Behavioral Avoidance Test; CGI: Clinical Global Impression; FEAS: Fragebogen zu Ekel und Angst vor Spinnen (questionnaire regarding disgust and fear of spiders); STAI: State Trait Anxiety Inventory; BDI-II: Beck Depression Inventory II; ASI-3: Anxiety Sensitivity Index; GSE: General Self Efficacy Scale.

[a] available for n = 43; [b] available for n = 44; [c] available for n = 44. Values given as mean (standard deviation) except where noted.

Table S5. Sample characteristics for the morphometry sample grouped by the magnitude of the within-session extinction (N = 87).

	high n = 44 (50.6%)	low n = 43 (49.4%)	χ^2 or *t* (df)	*p*
Demographic characteristics				
Age (years)	28.23 (8.52)	30.85 (10.61)	-1.14 (85)	0.256
Female gender [n (%)]	38 (86.36)	37 (86.05)	0.002 (1)	0.966
Years of education	14.66 (3.18)	14.00 (3.50)	0.92 (85)	0.360
Clinical and psychometric characteristics				
SPQ sum score	23.14 (2.67)	23.05 (2.01)	0.18 (79.83)	0.860
BAT final distance (cm)	168.98 (67.81)	175.01 (56.67)	-0.45 (85)	0.654
Duration exposure session (min)	83.34 (26.85)	89.74 (24.64)	-1.16 (85)	0.250
Within-session extinction	61.39 (11.01)	30.22 (11.78)	12.75 (85)	<0.001
Age of onset	9.07 (4.22)[a]	7.36 (3.73)[b]	1.98 (83)	0.051
Comorbidity [n (%)]	2 (4.55)	1 (2.33)	2.99 (2)	0.224
major depression	2 (4.55)	0 (0.00)		
subordinate animal phobia	0 (0.00)	1 (2.33)		
CGI [n (%)]			3.21 (3)	0.361
Mildly ill	8 (18.18)	7 (16.28)		
Moderately ill	15 (34.09)	17 (39.53)		
Markedly ill	18 (40.91)	19 (44.19)		
Severely ill	3 (6.82)	0 (0.00)		
FEAS anxiety	103.05 (12.28)[c]	100.14 (15.80)	0.95 (84)	0.344
FEAS disgust	111.37 (13.27)[d]	109.14 (10.47)	0.87 (84)	0.389
STAI- Trait	35.89 (9.79)	36.70 (8.21)	-0.42 (85)	0.677
BDI-II total	3.43 (4.26)	3.60 (4.26)	-0.19 (85)	0.850
ASI-3	16.07 (9.42)	15.05 (10.54)	0.48 (85)	0.635
GSE	2.97 (0.42)	2.90 (0.41)	0.79 (85)	0.434

SPQ: Spider Phobia Questionnaire; BAT: Behavioral Avoidance Test; CGI: Clinical Global Impression; FEAS: Fragebogen zu Ekel und Angst vor Spinnen (questionnaire regarding disgust and fear of spiders); STAI: State Trait Anxiety Inventory; BDI-II: Beck Depression Inventory II; ASI-3: Anxiety Sensitivity Index; GSE: General Self Efficacy Scale.

[a] available for n = 43; [b] available for n = 42; [c] available for n = 43; [d] available for n = 43. Values given as mean (standard deviation) except where noted.

3.3. SPF: Behavioral data according to group classification

The repeated-measures ANOVA with the within-subject factor condition and the between-subject factor SPQ (non-)responder (see figure S1) revealed again a significant main effect for condition (F (1.81, 141.19) = 467.43, p < 0.001), whereas the interaction condition x SPQ (non-)responder was non-significant (F (1.81, 141.60) = 0.68, p = 0.49).

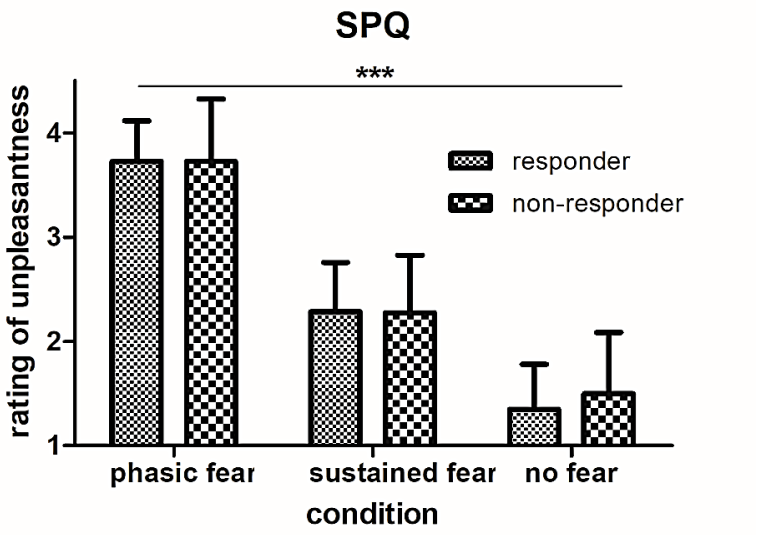

Figure S1. Behavioral ratings of the SPF task for the group SPQ (non-)responders. Ratings of pleasantness were collected for all three conditions. 1 = very pleasant, 2 = pleasant, 3 = unpleasant, 4 = very unpleasant. Means with standard deviation (SD) are displayed. SPQ: Spider Phobia Questionnaire. ***p < 0.001.

The repeated-measures ANOVA with the within-subject factor condition and the between-subject factor BAT (non-)responder (figure S2) revealed again a significant main effect for condition (F (1.82, 141.60) = 509.14, p < 0.001), whereas the interaction condition x BAT (non-)responder was non-significant (F (1.82, 141.60) = 0.09, p = 0.90).

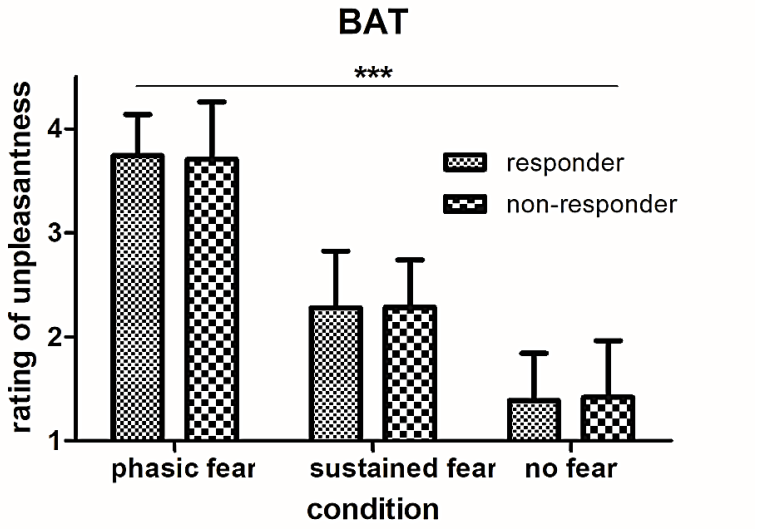

Figure S2. Behavioral ratings of the SPF task for the group BAT (non-)responders. Ratings of pleasantness were collected for all three conditions. 1 = very pleasant, 2 = pleasant, 3 = unpleasant, 4 = very unpleasant. Means with standard deviation (SD) are displayed. BAT: Behavioral Avoidance Test. ***p < 0.001.

The repeated-measures ANOVA with the within-subject factor condition and the between-subject factor ws extinction (figure S3) revealed again a significant main effect for condition (F (1.82, 141.90) = 511.63, p < 0.001), whereas the interaction condition x ws extinction was non-significant (F (1.82, 141.90) = 0.54, p = 0.57).

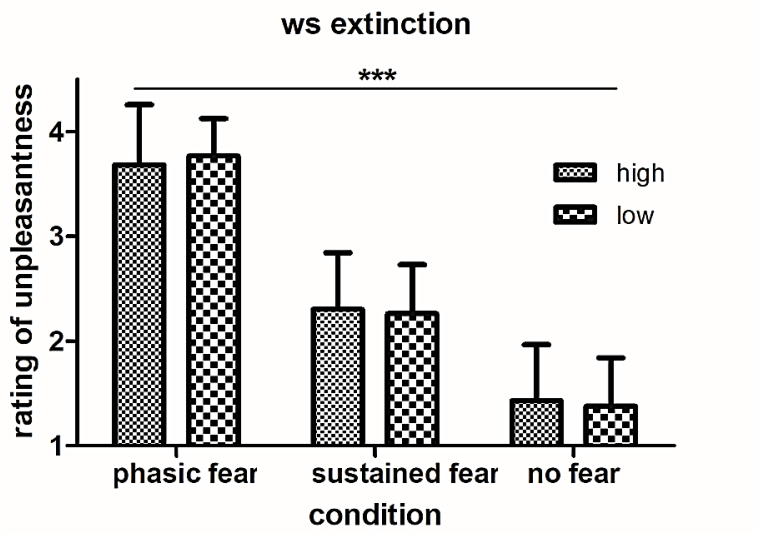

Figure S3. Behavioral ratings of the SPF task for the group ws extinction. Ratings of pleasantness were collected for all three conditions. 1 = very pleasant, 2 = pleasant, 3 = unpleasant, 4 = very unpleasant. Means with standard deviation (SD) are displayed. Ws extinction: within-session extinction. ***p < 0.001.

3.4. Whole-brain results: main task effects & main connectivity

Table S6. Brain activation patterns for the contrast phasic fear > no fear and main connectivity of the seed region based on the contrast phasic fear > no fear for the combined sample.

Contrast/region	side	voxels	x	y	z	*t*	*p*
Main task effects							
SPF: phasic fear > no fear							
Inferior occipital gyrus	L	19985	-36	-78	-6	22.95	<0.001
Middle occipital gyrus	L		-42	-80	2	21.51	<0.001
Calcarine sulcus	L		-10	-90	-2	21.51	<0.001
Hippocampus	L	1134	-20	-28	-4	17.53	<0.001
Hippocampus	L		-32	-24	-12	9.53	<0.001
Amygdala	L		-24	-4	-18	7.90	<0.001
Anterior cingulate cortex	R	380	2	18	26	7.74	<0.001
Supplementary motor area	R	85	10	2	74	7.44	<0.001
Precentral gyrus	R	34	54	0	50	6.64	<0.001
Cerebellum 8	R	65	28	-52	-48	6.21	<0.001
Insula	R	29	36	26	-2	6.20	<0.001
Cerebellum 8	R	54	16	-68	-40	6.05	<0.001
Supplementary motor area	R	13	4	8	64	5.37	0.003
Main connectivity							
PPI: seed region left amygdala (-24 -4 -18) and phasic fear > no fear							
Superior occipital gyrus	L	11296	-16	-94	20	8.57	<0.001
Inferior occipital gyrus	R		40	-58	-5	8.54	<0.001
Middle occipital gyrus	R		42	-80	10	8.40	<0.001
Hippocampus	R	12	28	-26	-8	5.75	<0.001

L: left; R: right; voxel: number of voxels per cluster; x, y, z: MNI coordinates; SPF: Sustained and phasic fear paradigm; PPI: psychophysiological interaction. Whole-brain results at $p < 0.05$ FWE-corrected with a minimum cluster size of $k_E = 10$ contiguous voxels.

3.5. Whole-brain results: group comparisons

Table S7. Functional and structural group analyses for the contrast phasic fear > no fear and functional connectivity of the seed region based on the contrast phasic fear > no fear.

Contrast/group/region	side	voxels	x	y	z	*t*	*p*
SPF: Differential functional activation: phasic fear > no fear							
SPQ responder > non-responder							
Lingual gyrus	L	17	-10	-74	-2	3.90	<0.001
SPQ non-responder > responder						no significant differences	
BAT responder > non-responder						no significant differences	
BAT non-responder > responder							
Medial superior frontal gyrus	R	151	6	30	60	4.84	<0.001
Superior parietal lobule	L	11	-24	-54	70	4.18	<0.001
Inferior temporal gyrus	R	16	56	-12	-26	4.11	<0.001
Midcingulate cortex	R	19	8	-26	28	4.05	<0.001
Superior frontal gyrus	L	34	-26	-4	64	3.97	<0.001
Supplementary motor area	L	32	-10	10	48	3.96	<0.001
Superior frontal gyrus	R	20	20	52	38	3.82	<0.001
Cerebellum 9	L	21	0	-52	-46	3.77	<0.001
Posterior cingulate cortex	R	13	10	-42	24	3.76	<0.001
Superior frontal gyrus	R	39	24	10	68	3.76	<0.001
Rolandic operculum	R	11	44	8	16	3.71	<0.001
Medial superior frontal gyrus	L	10	-6	48	26	3.65	<0.001
Middle frontal gyrus	L	10	-24	20	62	3.61	<0.001
Medial superior frontal gyrus	R	11	6	60	26	3.54	<0.001
Paracentral lobule	R	11	14	-28	60	3.49	<0.001
ws extinction high > low						no significant differences	
ws extinction low > high							
Inferior frontal operculum	R	56	46	18	16	4.13	<0.001
Inferior parietal lobule	L	57	-42	-40	54	4.00	<0.001
Precuneus	L	44	-10	-46	66	3.99	<0.001
Supramarginal gyrus	R	30	60	-22	40	3.93	<0.001
Middle frontal gyrus	L	20	-28	50	30	3.82	<0.001
Superior frontal gyrus	R	20	34	-6	60	3.77	<0.001
Supplementary motor area	L	17	-10	6	64	3.76	<0.001
Paracentral lobule	L	22	-10	-16	72	3.73	<0.001
Middle occipital gyrus	R	14	48	-72	26	3.71	<0.001
Supplementary motor area	R	12	12	16	60	3.68	<0.001
Precentral gyrus	L	22	-54	8	28	3.63	<0.001
Middle temporal gyrus	R	11	44	-62	10	3.63	<0.001

Table S7 (continued).

PPI: Differential functional connectivity: phasic fear > no fear[1]							
SPQ responder > non-responder							
Middle temporal gyrus		L	22	-58	-20	-6	4.02	<0.001
Middle temporal gyrus		L	39	-50	-68	20	3.94	<0.001
Superior temporal gyrus		R	15	66	-38	14	3.88	<0.001
Medial superior frontal gyrus		L	86	2	44	42	3.87	<0.001
Middle temporal gyrus		L	11	-50	2	-24	3.73	<0.001
Middle temporal gyrus		L	12	-36	-52	20	3.66	<0.001
Medial superior frontal gyrus		R	11	6	56	36	3.60	<0.001
Middle temporal gyrus		R	29	54	-52	6	3.57	<0.001
SPQ non-responder > responder							no significant differences	
BAT responder > non-responder							
Calcarine sulcus		R	20	26	-94	0	3.91	<0.001
Angular gyrus		L	16	-40	-50	30	3.85	<0.001
Middle temporal gyrus		L	35	-50	-48	4	3.82	<0.001
Superior temporal gyrus		R	30	52	-36	12	3.68	<0.001
BAT non-responder > responder							no significant differences	
ws extinction high > low							no significant differences	
ws extinction low > high							no significant differences	
Differences in grey matter volume (GMV)							
SPQ responder > non-responder							no significant differences	
SPQ non-responder > responder							
70%	Background	L	146	-9	-3	-9	4.04	<0.001
14.8%	Caudate nucleus	L						
13.5%	Thalamus	L						
1.5%	Pallidum	L						
BAT responder > non-responder							
Hippocampus[2]		R	261	24	-17	-23	3.71	<0.001
BAT non-responder > responder							no significant differences	
ws extinction high > low							no significant differences	
ws extinction low > high							
Middle frontal gyrus		R	151	30	54	24	4.07	<0.001
Inferior frontal operculum		L	267	-59	9	8	4.06	<0.001

[1] seed region: left amygdala, -24 -4 -18
[2] cluster encompassing right amygdala
L: left; R: right; voxels: number of voxels per cluster; x, y, z: MNI coordinates; SPQ: Spider Phobia Questionnaire; BAT: Behavioral Avoidance Test; ws extinction: within-session fear extinction; SPF: Sustained and phasic fear paradigm; PPI: psychophysiological interaction. Whole-brain results at $p < 0.001$ (uncorrected) with a minimum cluster size of $k_E = 10$ contiguous voxels for functional activation and functional connectivity analyses; for morphometric analysis k_E was determined empirically per group comparison ($k_E = 86$ for SPQ & BAT, $k_E = 85$ for ws extinction).

PUBLICATION LIST

Schwarzmeier, H., Kleint, N. I., Wittchen, H.-U., Ströhle, A., Hamm, A. O., & Lueken, U. (2019). Characterizing the nature of emotional-associative learning deficits in panic disorder: An fMRI study on fear conditioning, extinction training and recall. *European Neuropsychopharmacology, 29*(2), 306-318.

Schwarzmeier, H., Leehr, E. J., Böhnlein, J., Seeger, F. R., Roesmann, K., Gathmann, B., Herrmann, M. J., Siminski, N., Junghöfer, M., Straube, T., Grotegerd, D., & Dannlowski, U. (2020). Theranostic markers for personalized therapy of spider phobia: Methods of a bicentric external cross-validation machine learning approach. *International Journal of Methods in Psychiatric Research, 29*(2), e1791.

CURRICULUM VITAE

ACKNOWLEDGMENTS / DANKSAGUNG

AFFIDAVIT

I hereby confirm that my thesis entitled “From fear extinction to exposure therapy: neural mechanisms and moderators of extinction” is the result of my own work. I did not receive any help or support from commercial consultants. All sources and / or materials applied are listed and specified in the thesis.

Furthermore, I confirm that this thesis has not yet been submitted as part of another examination process neither in identical nor in similar form.

_____ _____

Place, Date Signature

EIDESSTATTLICHE ERKLÄRUNG

Hiermit erkläre ich an Eides statt, die Dissertation „Von der Furchtextinktion zur Expositionstherapie: Neuronale Mechanismen und Moderatoren der Extinktion“ eigenständig, d.h. insbesondere selbständig und ohne Hilfe eines kommerziellen Promotionsberaters, angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben.

Ich erkläre außerdem, dass die Dissertation weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat.

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