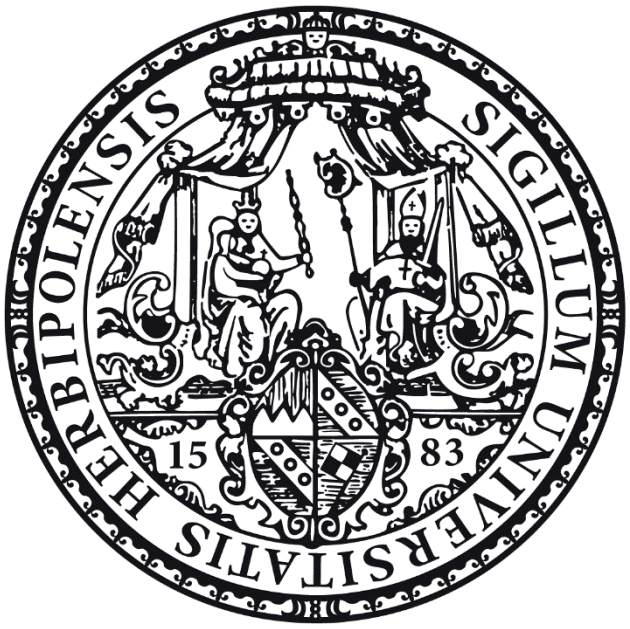

Moderators of exposure-based treatment outcome in anxiety disorders: an fMRI approach

Moderatoren des Expositionserfolgs bei Angststörungen: ein fMRT-basierter Ansatz

Doctoral thesis for a doctoral degree (Dr. rer. nat.)

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Abstract

Even though exposure-based cognitive behavioral therapy (CBT) constitutes a first-line treatment for anxiety disorders, a substantial proportion of patients does not respond in a clinically significant manner. The identification of pre-treatment patient characteristics that are associated with treatment outcome might aid in improving response rates. Therefore, the present doctoral thesis aimed at investigating moderators of treatment outcome in anxiety disorders: first, we investigated the neural correlates of comorbidity among primary panic disorder/agoraphobia (PD/AG) and secondary social anxiety disorder (SAD) moderating treatment outcome towards exposure-based CBT. Second, pre-treatment functional resting-state connectivity signatures of treatment response in specific phobia were studied.

Within the first study, we compared PD/AG patients with or without secondary SAD regarding their clinical and neurofunctional outcome towards a manualized CBT treatment focusing on PD/AG symptoms. Prior to treatment, PD/AG+SAD compared to PD/AG-SAD patients exhibited a specific neural signature within the temporal lobe, which was attenuated to the level of PD/AG-SAD patients afterwards. CBT was equally effective in both groups. Thus, comorbidity among those two anxiety disorders did not alter treatment outcome substantially. This might be due to the high overlap of shared pathophysiological features within both disorders.

In the second study, we assessed pre-treatment functional resting-state connectivity within a sample of spider phobic patients that were treated with massed in virtuo exposure. We found responders already prior to treatment to be characterized by stronger inhibitory frontolimbic connectivity as well as heightened connectivity between the amygdala and regions related to the ventral visual stream. Furthermore, patients demonstrating high within-session extinction exhibited pronounced intrinsic prefrontal connectivity. Our results point to responders exhibiting a brain prepared for the mechanism of action of exposure.

Taken together, results highlight the major impact of pre-treatment characteristics on treatment outcome. Both, PD/AG+SAD patients as well as responders within the SpiderVR study exhibited heightened activation or connectivity within the ventral visual pathway and the amygdala. Pronounced visual processing together with enhanced executive control and emotion regulation seem to constitute a fruitful soil for successful exposure. The results provide starting points for personalized treatment approaches in order to improve treatment success in the anxiety disorders. Future studies are needed to investigate the benefit of neuroscientifically informed CBT augmentation strategies such as repetitive transcranial magnetic stimulation.

Zusammenfassung

Obwohl expositionsbasierte kognitive Verhaltenstherapie (KVT) bei Angststörungen als Behandlungsmethode der Wahl gilt, profitieren viele Patient*innen nicht in klinisch bedeutsamer Weise. Durch die Identifikation von Patient*innenmerkmalen mit Bezug zum Therapieerfolg bereits vor Behandlungsbeginn könnte das Therapieansprechen verbessert werden. Die vorliegende Arbeit hat sich daher die Identifikation von Moderatoren des Behandlungserfolgs zum Ziel gesetzt. Zunächst untersuchten wir die neuronalen Korrelate einer Komorbidität zwischen Panikstörung/Agoraphobie und sozialer Phobie (SAD) und deren moderierenden Einfluss auf den Behandlungserfolg. Daneben wurden Merkmale der funktionellen Ruhe-Konnektivität, die mit dem Therapieerfolg bei spezifischer Phobie in Zusammenhang stehen, untersucht.

In der ersten Studie untersuchten wir Panikpatient*innen mit und ohne sekundäre SAD in Bezug auf ihr klinisches und neurofunktionelles Behandlungsergebnis unter Anwendung einer manualisierten KVT. Panikpatient*innen mit sekundärer SAD zeigten vor Therapiebeginn im Vergleich zu Panikpatient*innen ohne SAD ein spezifisches Aktivierungsmuster im Temporallappen, welches sich nach der Behandlung dem der Patient*innen ohne SAD anglich. Die KVT war in beiden Gruppen gleich erfolgreich. Die Ergebnisse deuten darauf hin, dass eine Komorbidität hier keinen substanziellen Einfluss auf den Therapieerfolg hat. Dies könnte in der überlappenden Pathophysiologie begründet sein.

In der zweiten Studie untersuchten wir die funktionelle Ruhe-Konnektivität bei Spinnenphobiker*innen, die anschließend mit einer massierten Expositionstherapie in virtueller Realität behandelt wurden. Therapie-Responder waren hierbei durch eine verstärkte inhibitorische fronto-limbische Konnektivität vor Therapiebeginn sowie eine ebenfalls verstärkte Kopplung von Amygdala und Regionen des ventralen Objekterkennungspfades gekennzeichnet. Zugleich wiesen Patient*innen mit hoher within-session Extinktion eine verstärkte intrinsische präfrontale Konnektivität auf. Die Ergebnisse deuten auf eine verbesserte neuronale Vorbereitung auf inhibitorisches Lernen bei Patient*innen mit gutem Therapieansprechen hin.

Zusammenfassend unterstreichen die Ergebnisse die Relevanz von Patient*inneneigenschaften für den Therapieerfolg. Sowohl Panikpatient*innen mit sekundärer SAD als auch die Responder der SpiderVR-Studie wiesen erhöhte Aktivierung bzw. Konnektivität zwischen der Amygdala und dem ventralem Objekterkennungspfad auf. Zusammen mit einer stärkeren exekutiven Kontrolle und Emotionsregulation scheint eine verstärkte visuelle Verarbeitung einem guten Therapieerfolg dienlich zu sein. Die Behandlungsergebnisse könnten auf Basis neurowissenschaftlicher Erkenntnisse durch den Einsatz zusätzlicher Methoden wie der repetitiven transkraniellen Magnetstimulation verbessert werden.

1 Introduction

Pieter Bruegel the Elder (1557): *Parable of the Sower*. Oil on wood panel, Timken Museum of Art, San Diego, CA, USA.[1]

„Hearken; Behold, there went out a sower to sow: And it came to pass, as he sowed, some fell by the way side, and the fowls of the air came and devoured it up. And some fell on stony ground, where it had not much earth; and immediately it sprang up, because it had no depth of earth: But when the sun was up, it was scorched; and because it had no root, it withered away. And some fell among the thorns, and the thorns grew up, and choked it, and it yielded no fruit. And other fell on good ground, and did yield fruit that sprang up and increased; and brought forth, some thirty, and some sixty, and some an hundred."

The Gospel of Mark 4, 3-8 (Carroll & Prickett, 2008)

The quotation out of the Gospel of Mark encompasses the main passage of the so-called "Parable of the Sower". It is said to be recited by Jesus on a boat in Capernaum at the Sea of Galilee and is considered one of the most well-known as well as fundamental biblical parables

[1] Image courtesy of the Putnam Foundation and Timken Museum of Art, San Diego, CA, USA.

(Gerhardsson, 1968). This is further highlighted by its frequent reception in the fine arts e.g. within the eponymic painting of Pieter Bruegel the Elder who illustrated the scene in 1557.

Referring to its literal meaning, crops highly depend on the ground where the seed is sown. If the ground is fruitful, crops will be rich, whereas crops will be poor if the ground is inappropriate for the respective seed. By means of this parable, Jesus metaphorically refers to the people, who are listening to God's tidings of joy. Depending on the individual openness (represented by the different grounds) to the religious message (represented by the seed), one would benefit more or less from its content (represented by the crop). The parable thus paradigmatically highlights the immense impact that preconditions may exert on the outcome of the very same action.

Outside this biblical framework, such dependencies of certain preconditions and observed outcomes are frequent as well. This is especially true within medicine where they are of high interest due to so-called predispositions being a potential target for the prevention of diseases. Predispositions are defined as "a propensity in a person to respond or react in a certain way" (Oxford English Dictionary Online, 2020). However, predispositions - which can be seen as an analogue of the different grounds within the parable - are not only relevant with respect to the development of a disease. There are also predispositions that relate to treatment outcome in various disorders. For example, a propensity to thrombo-inflammation has been identified as a potentially predisposing factor with respect to worse treatment outcome in acute ischaemic stroke (Stoll & Nieswandt, 2019). Similarly, obesity has been related to worse laparotomy outcomes in patients suffering from abdominal trauma (Fu et al., 2019). The identification of such pre-treatment characteristics that moderate treatment outcome might aid in patient stratification and thus the development of personalized treatment options. Furthermore, the predisposing factors may be used as targets for additional or modified treatments in order to improve response rates.

Mental health is a discipline where treatment is often associated with enormous expenditure of time and money (Wittchen et al., 2011). Therefore, lacking treatment response e.g. due to a misfit of patients' predispositions and treatments' characteristics bears even more potential of frustration for clinicians as well as patients, respectively. This is especially true for anxiety disorders, which constitute the most frequent group of mental disorders and have been shown to be accompanied by high disease burden (Kessler et al., 2012; Wittchen et al., 2011). Moreover, roughly 50% of anxiety disorder patients do not achieve remission or experience relapse after successful treatment (Loerinc et al., 2015). This lack of response, which is observed in a

substantial portion of anxiety disorder patients, might at least partly be due to patients' pre-treatment characteristics (Lueken et al., 2016).

Therefore, this doctoral thesis aims to investigate different moderators of treatment response: first, we address the issue of comorbidity, including its neural substrates, and its effect on treatment outcome. Second, we focus on resting-state connectivity as a pre-treatment neurobiological marker related to treatment outcome in anxiety disorders. In order to explore those research questions, two separate studies on anxiety disorder patients have been conducted, each of them focusing on neural signatures and their relation to treatment outcome. In terms of the parable, there might be neural signatures representing more or less fruitful soil, thus resulting in richer or poorer outcome to exposure-based psychotherapy.

Before explicitly referring to the two studies and the methodology that was used to address the above-mentioned research questions, the hypotheses and results, this thesis aims to give an introduction and overview of their shared theoretical background. This includes the symptomatology and pathomechanisms as well as the treatment of anxiety disorders with a special focus on panic disorder, social anxiety disorder, arachnophobia, and their neural correlates. Furthermore, mechanisms and efficacy of exposure-based CBT as a first-line treatment for all anxiety disorders will be explained.

2 Theoretical background

2.1 Anxiety disorders

2.1.1 Diagnostic classification and epidemiology

With a twelve-month prevalence of 14%, anxiety disorders constitute the most frequent form of psychiatric conditions (Wittchen et al., 2011). This is reflected in roughly 69.1 million affected individuals across Europe (Wittchen et al., 2011). Anxiety disorders are characterized by exaggerated or unreasonable apprehensions that elicit marked fear and usually result in avoidance behavior (Beck & Haigh, 2014; Clark & Beck, 2010; Craske et al., 2017; Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014). Epidemiological studies indicate anxiety disorders to be associated with high disease burden and immense socioeconomic cost (Ezzati et al., 2002; Gustavsson et al., 2011; Olesen et al., 2012; Vos et al., 2012; Wittchen et al., 2011). They have been shown to impair various areas of life including education, marriage stability, parental functioning, employment status, work ability and financial success (Butterworth & Rodgers, 2008; Kawakami et al., 2012; Knappe et al., 2009; Lee et al., 2009; Lund et al., 2010) and thus rank among the leading causes of disability (Whiteford et al., 2013). Those findings might relate to the comparatively early onset of anxiety disorders with a median age of 11 years (Beesdo-Baum & Knappe, 2012; Kessler et al., 2005). Even though anxiety disorders start early, latency to seek treatment is often very long and consultation rates of health professionals are low (Brugha et al., 2004). This frequently results in chronification (DSM-IV-TR, 2000). Moreover, comorbidity rates are high. Most of the comorbid conditions are other anxiety disorders, followed by affective and substance-use disorders (DSM-V, 2013). Frequently, the anxiety disorders precede those comorbidities (Meier et al., 2015). Besides psychiatric comorbidities, anxiety disorders also often co-occur with somatic conditions like asthma or cardiovascular diseases (DSM-V, 2013).

Taken together, those findings highlight the major relevance of research on effective and efficient treatments for anxiety disorders. As this doctoral thesis will especially focus on panic disorder, social anxiety disorder and spider phobia as a subtype of specific phobia, those anxiety disorders should be considered in a more detailed way within the following paragraphs.

Panic disorder (PD; DSM-IV-TR 300.01) is characterized by recurrent states of unexpected intense fear that are commonly referred to as panic attacks. Those attacks cannot be immediately linked to a specific situation or certain circumstances and are thus perceived as

unpredictable. A panic attack itself is defined as a discrete episode of intense fear or distress that starts abruptly and reaches its maximum within ten minutes. Panic attacks last for a short period of time and are accompanied by symptoms like palpitations, sweating, breathing distress, thoracic pain or discomfort, derealization or depersonalization and fear of dying, losing control or going crazy. Frequently, concerns about the consequences of the attacks or fear of suffering from further attacks are present. The latter usually leads to marked avoidance behavior. (DSM-IV-TR, 2000).[2]

PD and agoraphobia frequently appear together. Agoraphobia (AG; DSM-IV-TR 300.22; from ancient greek ἀγορά *agorá*, engl. 'Market' or 'public Place', and φόβος *phobos*, engl. 'Fear') is diagnosed if the patient exhibits anxiety about being in public places or situations from which escape might be impossible, difficult or embarrassing or in which help may be unavailable. Such situations typically involve being outside home alone, being in a crowd, standing in a queue, driving by car or traveling with public transport. Patients try to avoid those situations or endure them only with marked distress or anxiety about having a panic attack or panic-like symptoms. This may also require them to be accompanied by another person. Exclusive AG is only diagnosed if the criteria of a PD have never been met previously. Otherwise, a panic disorder with agoraphobia (DSM-IV-TR 300.21) is diagnosed (DSM-IV-TR, 2000).

PD is estimated to affect about 2-3% of the population within one year. Roughly, one third of PD patients also meet the criteria of an AG and are thus diagnosed with panic disorder with agoraphobia. Prevalence estimates of AG vary across studies by 1.7% but there is consensus that only a small proportion of patients is meeting the criteria for AG without meeting the criteria for PD simultaneously. Among anxiety disorders, panic disorder with or without agoraphobia (PD/AG) starts comparatively late with a median age between 17-24 years. Women are affected about twice as often as men are. PD/AG is associated with high disease burden as it often significantly interferes with patients' daily life. Nevertheless, latency to seek psychiatric or psychotherapeutic treatment is often particularly long among PD/AG patients. They frequently misinterpret their symptomatology as caused by a somatic disorder and consequently consult e.g. a cardiologist first. Due to the high disease burden, comorbidity with other anxiety

[2] All diagnostic criteria mentioned within this dissertation thesis rely on the DSM-IV-TR classification of mental disorders (DSM-IV-TR, 2000). Due to the lack of a German translation of the Structured Clinical Interview for DSM-V (SCID) at the time of study setup, the existing German translation of DSM-IV SCID (Wittchen, Wunderlich, Gruschwitz, & Zaudig, 1997) was chosen to diagnose patients included in the investigations presented here.

disorders, major depression, or substance-use disorders is also frequent (DSM-IV-TR, 2000; DSM-V, 2013).

According to DSM-IV-TR diagnostic criteria, social anxiety disorder (SAD; DSM-IV-TR 300.23) is characterized by marked and persistent fear in social or performance situations in which the person is the focus of attention of unfamiliar people or exposed to potential scrutiny by others. The individual is afraid of behaving humiliatingly or embarrassingly and confrontation with the feared situations provokes marked fear that can also reach the form of a panic attack. The affected person is aware that the fear is unreasonable or exaggerated. Nevertheless, the situations are avoided or endured only with intense anxiety or distress. Due to the avoidance behavior, anxious anticipation or distress, affected individuals are significantly impaired within their normal routine, (academic) functioning, social activities or relationships, or there is marked distress about having the phobia (DSM-IV-TR, 2000).

12-month prevalence estimates of SAD range from 0.5-2%. Public speaking is the most common feared situation among SAD patients. Due to the high relevance of social skills and performance in social situations within our daily lives, SAD patients suffer from a high emotional burden, often underachieve at work or in academics and thus have a heightened risk for unemployment, loneliness as well as heightened rates of suicidal ideation. Median age of onset is 13 years. Frequent comorbidities are again other anxiety disorders, mood disorders, substance-use disorders, but also body dysmorphic disorder and avoidant personality disorder. Women are affected about 1.5 to 2 times more often than men (DSM-IV-TR, 2000; DSM-V, 2013).

Arachnophobia (from ancient greek ἀράχνη *arachne*, engl. ‚Spider', and φόβος *phobos*, engl. ‚Fear') is defined as a psychiatric condition of pathological fear evoked by the presence of joint-legged invertebrate animals, so called arachnids, such as spiders or scorpions. According to DSM-IV-TR diagnostic criteria, arachnophobia constitutes a subtype of specific phobia (DSM-IV-TR 300.29). Specific phobia is characterized by marked fear that is cued by the presence or anticipation of a certain object or situation. The symptomatology usually increases with increasing proximity of the feared stimulus. Exposure to the phobic stimulus immediately provokes an anxiety response, which may take the form of a panic attack. The affected individual is aware that the fear is exaggerated or unreasonable. However, the phobic situation is avoided or only endured accompanied by intense anxiety and discomfort. As for SAD, the patient's normal routine, (academic) functioning or social activities or relationships are significantly impaired. Besides the subtype of animal phobias, specific phobia can be divided into four further

subtypes: natural environment, blood-injection-injury, situational, and other (DSM-IV-TR, 2000).

Specific phobias constitute the most frequent form of anxiety disorders with a 12-month prevalence of approximately 7-9%. However, only 12-30% of all patients seek professional help. Among animal phobias, spider phobia constitutes the greatest proportion. About 75-90% of all animal phobia patients are of female gender and the vast majority report the disorder to have started during childhood between the ages of seven to eleven. In contrast to the situative subtype, prevalence rates of animal phobias decrease with age. Nevertheless, specific phobias often precede other anxiety disorders that usually have a later onset. Furthermore, there are high comorbidity rates with those disorders e.g. 44% for SAD or 27% for AG. Moreover, studies indicate the risk of developing other mental disorders like depression, bipolar disorder or substance use disorders to be increased two- to fourfold in individuals suffering from specific phobia (Castagna, Nebel-Schwalm, Davis Iii, & Muris, 2019; DSM-IV-TR, 2000; DSM-V, 2013).

2.1.2 Defensive networks in the brain

Anxiety disorders are characterized by a pathological amount of anxiety as well as maladaptive defensive reactions that lead to emotional burden and disability (Craske et al., 2017; Wittchen et al., 2011). However, non-pathological anxiety and its associated defensive reactions substantially aid in ensuring safety and survival as they motivate and prepare the individual to defend its integrity or avoid a threatening situation (Lang, Davis, & Öhman, 2000; LeDoux, 2000; Marek & Sah, 2018). The behavioral component of anxiety is called the fight-or-flight response (Plutchik, 1984). Due to this protective function of anxiety, its development is thought to be related to evolutionary reasons (Darwin & Prodger, 1998; Plutchik, 1982). Anxious individuals were probably more likely to survive and thus also to reproduce themselves than non-anxious ones. The evolutionary emergence is further supported by the fact that defensive behaviors can be observed within a variety of species like non-human primates, rodents or birds (LeDoux, 2012; J. LeDoux & Daw, 2018; Mobbs, Hagan, Dalgleish, Silston, & Prévost, 2015; Plutchik, 1980).

Besides defensive behaviors in terms of the fight-or-flight response, anxiety is accompanied by cognitive changes (e.g. focusing of attention) as well as various bodily symptoms (e.g. acceleration of heart rate and respiration, rise of blood pressure), which facilitate the exe-

cution of defensive reactions (Barlow, 2002). Anxiety is thought to orchestrate those multimodal processes to ensure optimal coping with imminent threat (Barlow, 2002). The underlying regulatory instance, which is responsible for the initiation and balancing of all anxiety-related responses, is the brain. Therefore, numerous studies have investigated the so-called defensive system network within the brain of humans as well as animals. It consists of the amygdala, insula and anterior cingulate cortex (ACC) as principal brain regions (Fanselow, 1994; Sehlmeyer et al., 2009; Shin & Liberzon, 2010). However, other regions like the prefrontal cortex (PFC), periaqueductal grey (PAG), (hypo-)thalamus and hippocampus are involved as well (Fanselow, 1994; Sehlmeyer et al., 2009; Tovote, Fadok, & Lüthi, 2015). Within this network, the amygdala appears to be the key structure (Davis & Whalen, 2001; Fanselow, 1994; LeDoux & Daw, 2018; LeDoux, 2000). Across species, it has been demonstrated to be strongly activated when being confronted with a threatening situation (Maren, 2008; Shin & Liberzon, 2010). The amygdala is considered to be especially relevant in the evaluation of threat (LeDoux, 2000). Its role within the defensive system network is further supported by lesion studies, which suggest defensive behaviors to decrease when the amygdala is damaged. There are corresponding findings with respect to amygdala damage in animals (Oakes & Coover, 1997; Phillips, 1964) as well as humans (Adolphs, Tranel, Damasio, & Damasio, 1994). Accordingly, a stimulation of the amygdala has been demonstrated to result in exaggerated defensive responses (Gloor, 1955).

The defensive system was also studied within a network perspective thus including the connectivity between the mentioned structures. LeDoux (1996) investigated the structural pathways and connections that transfer threatening environmental information to the amygdala and thereby to the defensive system. He was able to identify a “high” and “low road” transmitting information on emotional stimuli to the amygdala. Both roads start from the sensory thalamus, which is considered the main relay structure for sensory information in the brain. The low road directly connects to the amygdala, whereas on the high road the emotional information is first transmitted to the sensory cortex where it is processed and subsequently reaches the amygdala. LeDoux (1996) proposed the direct thalamo-amygdala pathway to allow for reacting to a potentially dangerous stimulus even before consciously knowing what it is. As the low road bypasses the cortex, it is shorter and faster. However, this also results in a coarser representation of the stimulus, which may lead to misinterpretations. Conversely, the high road leads to a more elaborated processing of the stimulus, which is slower but also more precise (LeDoux, 1996).

Today, magnetic resonance imaging (MRI) techniques allow to further clarify the neural connectivity within the defensive system thus extending the basic work of LeDoux. On the one hand, MRI techniques enable the study of structural connectivity within the rodent as well as human defensive system (see e.g. Freese & Amaral, 2009; LeDoux, 2000; Tovote et al., 2016; Tovote et al., 2015). On the other hand, functional MRI (fMRI) allows to investigate "the temporal dependency of neuronal activity patterns of anatomically separated brain regions" (Aertsen, Gerstein, Habib, & Palm, 1989; Van Den Heuvel & Pol, 2010), which is called functional connectivity (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995). If the measurement of functional connectivity is conducted in the absence of a specific task, one refers to resting state functional connectivity (rsFC; Biswal, 2012). The underlying assumption is that brain regions that frequently work together also form a functional network at rest, which is characterized by correlated spontaneous neuronal activity (Smith et al., 2013; Van Den Heuvel & Pol, 2010). This is also true for the regions within the defensive system. The amygdala has been shown to exhibit positive connectivity with ACC, insula, medial prefrontal cortex (MPFC), striatum and thalamus at rest and is thus functionally connected with the main defensive system structures (Roy et al., 2009).

2.1.3 Fear conditioning as translational model and transdiagnostic pathomechanism

To ensure the protective function of the defensive system it is highly relevant that information on new threatening stimuli or situations can be integrated. This adaptive ability is represented by learning mechanisms, which allow for the acquisition of fear (Fullana et al., 2016). Three different pathways were described: Fear can be acquired via observational (see e.g. Dymond, Schlund, Roche, De Houwer, & Freegard, 2012; Mineka & Zinbarg, 2006; Olsson & Phelps, 2007) and semantic learning (see e.g. Mineka & Zinbarg, 2006; Olsson & Phelps, 2007) as well as through fear conditioning. The latter is considered a translational as well as transdiagnostic model in anxiety disorders (Milad & Quirk, 2012; Norton & Paulus, 2017; Scheveneels, Boddez, & Hermans, 2019).

Fear conditioning is based on the findings of Ivan P. Pavlov who first described the principles of classical conditioning during the first half of 20th century (Pavlov, 1927). He repetitively paired the ringing of a bell (conditioned stimulus; CS) with the presentation of food (unconditioned stimulus; US) to a dog. Previously, only the presence of food led to salivation

(unconditioned response; UR). After this procedure, which is now called classical conditioning, the ringing of the bell was sufficient to cause salivation even though no food was presented to the dog (conditioned response; CR). Henceforth, classical conditioning has been extensively studied in animals as well as humans and became the fundamental basis of learning theory (Cryan & Holmes, 2005; Fanselow & Poulos, 2005; Fullana et al., 2016; Lang et al., 2000; Milad, Rauch, Pitman, & Quirk, 2006; Sehlmeyer et al., 2009; Watson & Rayner, 1920).

Fear conditioning in turn is defined as "a Pavlovian conditioning procedure with an aversive stimulus as US and fear measures as dependent variables (CR)" (Vervliet, Craske, & Hermans, 2013, p. 218). Like classical conditioning, it has also been studied in animals first. Pavlov (1927) was also interested in such defensive reactions. Therefore, he paired the sound of a metronome with the taste of diluted acid and subsequently observed his dog to shake his head and move his tongue as if to expel the acid even when only the sound was presented. Neurally, fear conditioning in rodents has been shown to involve the amygdala as a key structure of the defensive system (Fanselow & Poulos, 2005), which receives its inputs via the high and low road (LeDoux, 1996; LeDoux, 2000). The CS-US association is thought to be formed within the basolateral amygdala and fear responses are subsequently initiated via the central nucleus (Milad & Quirk, 2012; Vervliet et al., 2013). Meta-analytic evidence further suggests fear conditioning in rodents to be associated with a neural circuitry comprising the nucleus accumbens (including the bed nucleus of the stria terminalis, BNST), hippocampus, ventromedial hypothalamus, PAG, several brain stem and thalamic nuclei, the insular cortex, as well as the prelimbic and infralimbic cortex (Michael Davis, 2006; Maren, 2008; Quirk & Mueller, 2008). The latter two are considered homologues of the human dorsal ACC and ventromedial prefrontal cortex (VMPFC; VanElzakker, Dahlgren, Davis, Dubois, & Shin, 2014).

The mentioned regions identified in rodents substantially overlap with the brain areas that have been related to human fear conditioning (Fullana et al., 2016; Sehlmeyer et al., 2009). However, the picture is considerably more complicated in humans: The meta-analysis of (Sehlmeyer et al., 2009) has identified the amygdala (see also Shin & Liberzon, 2010), insular cortex and ACC to be consistently involved in the acquisition of fear. Additionally, they stated out that some studies also reported activation within the hippocampus, posterior cingulate cortex (PCC), dorsolateral prefrontal cortex (DLPFC), and VMPFC. A more recent meta-analysis by Fullana et al. (2016) again found functional brain activation within the anterior insular cortex, (dorsal) ACC, and DLPFC, but also within the dorsal pons, dorsal precuneus, hypothala-

mus, secondary somatosensory cortex, supplementary motor area, thalamus, and ventral striatum to be associated with human fear conditioning. However, there was no meta-analytic evidence for the amygdala within the human fMRI studies analyzed by Fullana et al. (2016). Functional deactivations upon the CS+ (CS associated with the US) compared to the CS- (CS not associated with the US) were found within the angular gyrus, anterior PFC, PCC, parahippocampal formation, and primary somatosensory cortex (Fullana et al., 2016).

Taken together, studies indicate structures of the defensive system network (also "fear network", see Sehlmeyer et al., 2009), which includes e.g. the amygdala, insula, and ACC, accompanied by memory-relevant structures (e.g. hippocampus) as well as brain regions related to executive control (e.g. PFC) to be involved in human as well as rodent fear conditioning. Due to the strong overlap of the neural circuitry in animals as well as humans, fear conditioning represents a strong translational model for the acquisition of fear. Additionally, it is considered to be a model for the pathogenesis of anxiety disorders (Duits et al., 2015; Fullana et al., 2016; Watson & Rayner, 1920). This is due to fear conditioning explaining how stimuli that are entirely or predominantly innocuous (e.g. certain bodily symptoms, narrow rooms, crowded places, spiders, talking in front of others) can elicit pathological fear. They have been paired at least once with aversive or even traumatic experiences (US; e.g. panic attack, being hurt or bitten, being laughed at) and thus acquired the properties of a CS. Anxiety disorder patients are thought to be characterized by facilitated acquisition of such CS-US associations (Duits et al., 2015).

Furthermore, conditioning mechanisms also explain how the pathological defensive reactivity to the CS persists even in the absence of CS-US contingency. Within the two-factor theory by Mowrer (1947) classical conditioning is considered to elicit phobic fear, whereas the fear is maintained via operant conditioning mechanisms. Operant conditioning, which was also initially studied within animals (Skinner, 1963), is considered the underlying mechanism leading to recurrent states of anxiety when being confronted with the feared object or situation. It is defined as the modification of the likelihood of a certain behavior (response, R) by means of its appetitive or aversive outcome (O). The resulting process is called reinforcement. This can nicely be illustrated via the example of a spider phobic patient: Once the individual has acquired the fear of spiders and related concerns, subsequent confrontations with a spider elicit an unpleasant emotional state of anxiety, which is accompanied by defensive reactions. To reduce this aversive feeling most individuals tend to avoid the spider e.g. by leaving the room. The subsequent reduction of fear is perceived as positive (O). This learning experience reinforces

the fear as well as the avoidance behavior (R). By means of negative reinforcement, avoidance becomes the key maintaining factor in anxiety disorders (Mowrer, 1947). Moreover, the individual is preserved from reevaluating its concerns (i.e. CS-US association) regarding spiders. This results in a vicious cycle of recurrent fear and avoidance that can be transferred to all anxiety disorders (Pittig, Wong, Glück, & Boschet, 2020). Neurally, operant conditioning and reinforcement are associated with cortico-striatal loops involving dopamine-rich brain regions like the ventral striatum, thalamus, insula and caudate (Chase, Kumar, Eickhoff, & Dombrovski, 2015).

Due to conditioning being involved in the etiology as well as maintenance of anxiety disorders, it also condenses within the neural substrates of those disorders (Lissek et al., 2005; Sehlmeyer et al., 2009). Neurofunctional studies in anxiety disorders again highlight the important role of the amygdala as a core structure (Duval, Javanbakht, & Liberzon, 2015; Shin & Liberzon, 2010). Compared to healthy controls, it seems to be hyperresponsive in anxiety disorder patients (Duval et al., 2015). The same is true for the ACC and Insula (Duval et al., 2015; Etkin & Wager, 2007). The ACC has been related to various psychological processes such as attention allocation (Luks, Simpson, Feiwell, & Miller, 2002), impulse control (Bauer et al., 2018) or social decision making (Lockwood & Wittmann, 2018). With respect to anxiety disorders, it seems to be relevant in the regulation of approach and avoidance during fear acquisition (Buchanan & Powell, 1982) and modulates fear expressions (Milad, Quirk, et al., 2007). The insula has been related to subjective feelings and emotion processing in general and is thus involved in the perception and expression of various emotions (Phan, Wager, Taylor, & Liberzon, 2002). Even though ACC and insula have been shown to be hyperresponsive in anxiety disorder patients, the findings regarding those two regions are more inconsistent compared to the amygdala. The hyperresponsivities are accompanied by hyporesponsivity in frontal structures like the VMPFC, which was however only robustly shown in post-traumatic stress disorder (PTSD; Etkin & Wager, 2007; Shin & Liberzon, 2010). Additionally, aberrant functioning of the hippocampus has been observed in anxiety disorders (Etkin & Wager, 2007; Shin & Liberzon, 2010).

A growing body of research also demonstrates significant resting-state connectivity alterations in anxiety disorder patients compared to controls. The vast majority of those studies focuses on SAD, generalized anxiety disorder (GAD), and PD/AG. Anxiety disorders are associated with aberrant connectivity within and between several large-scale resting-state networks. Those are the affective network (AN), salience network (SN), executive control network (ECN;

also fronto-parietal network, FPN), default mode network (DMN) and ventral attention network (VAN; Kim et al., 2011; Sylvester et al., 2012; Xu et al., 2019). The AN comprises the ACC, amygdala, nucleus accumbens, hypothalamus, hippocampus, OFC and (anterior) insula (Sheline, Price, Yan, & Mintun, 2010). The SN is thought to incorporate the (dorsal) ACC and orbitofrontal insular cortices (Seeley et al., 2007). The ECN comprises dorsolateral frontal and parietal brain regions (Seeley et al., 2007) whereas the DMN comprises medial frontal as well as medial and lateral parietal structures (Raichle, 2015). The VAN consists of the right ventrolateral PFC (VLPFC) and the right temporo-parietal junction (Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000; Corbetta, Patel, & Shulman, 2008).

It has been suggested that anxiety disorders are characterized by hypoconnectivity between AN, ECN and DMN as well as functional decoupling of DMN and ECN (Kim et al., 2011; J. Xu et al., 2019). Furthermore, increased functioning of the VAN and SN is accompanied by decreased functioning of the DMN and ECN in anxiety disorders (Sylvester et al., 2012). More specifically, SAD patients exhibit increased right amygdala seed-to-voxel connectivity with the left middle temporal gyrus (MTG), left supramarginal gyrus and left lateral occipital cortex (Pannekoek et al., 2013). Additionally, within the SN the bilateral ACC was correlated more positively with the left precuneus and left lateral occipital cortex (Pannekoek et al., 2013). No DMN alterations were found (Pannekoek et al., 2013). Geiger et al. (2016) found enhanced positive connectivity between left amygdala seed and left OFC in SAD patients, whereas Hahn et al. (2011) demonstrated reduced connectivity between those areas in SAD patients. Moreover, decreased connectivity within the visual network was shown among SAD patients (Liao et al., 2010). In PD, increased functional connectivity between right amygdala seed and bilateral precuneus as well as altered connectivity of the dorsal ACC seed with frontal, parietal and occipital areas has been revealed (Pannekoek et al., 2013). Similarly, also connectivity between perigenual ACC seed and precuneus seems to be increased in PD (Shin et al., 2013). For GAD increased voxel-to-voxel connectivity between hippocampus and fusiform gyrus (Cui et al., 2016) as well as decreased connectivity between amygdala seed, ACC and supramarginal gyrus (Makovac et al., 2016) have been proposed. Overall, anxiety disorders seem to be characterized by decreased functioning of regulatory networks (Xu et al., 2019).

2.1.4 The therapeutic learning process of extinction

The previous paragraphs have shown fear conditioning to be substantially involved in the development as well as maintenance of anxiety disorders, which is also reflected within their neural correlates. Deduced from this knowledge, the reversal of fear conditioning should lead to symptom attenuation within anxiety disorder patients (Jones, 1924; Watson & Rayner, 1920; Wolpe, 1958). Learning theory proposes CS-US associations to be attenuated via the repeated presentation of the CS without the US (Rachman, 1989). This process is called extinction and was also first described by Pavlov (1927). Extinction occurs if there is a reduction in the predictive value of the CS with respect to the occurrence of the US (Myers & Davis, 2007). However, extinction does not delete the original CS-US association (Myers & Davis, 2007; Sewart & Craske, 2020). Instead, it is considered to lead to the formation of a new CS-noUS association, which inhibits the previously acquired CS-US association (Bouton, 1993; Bouton & King, 1983; Milad & Quirk, 2012; Sewart & Craske, 2020).

One must distinguish several processes, which are related to extinction: First, the acquisition of the inhibitory CS-noUS association is often referred to as extinction training. Second, the decline of fear responses during extinction training is called within-session extinction (WS-ext). Third, the decrement of fear responses after a certain interval following extinction training is referred to as extinction retention or extinction recall. Unfortunately, extinction is not generally permanent. Several mechanisms can lead to the reoccurrence of extinguished fear responses. Those are reinstatement, renewal and spontaneous recovery. Reinstatement refers to the reappearance of conditioned fear responses after the unsignaled presentation of the US at some timepoint after extinction training. Renewal can occur when extinction recall is tested within a new context, which is different to the extinction training context. Spontaneous recovery refers to the reappearance of the extinguished fear responses at some timepoint following extinction training (Myers & Davis, 2007; Rescorla, 1988).

Within animal research, fear extinction and its related processes have been extensively studied, especially with respect to their neural basis (Milad & Quirk, 2012; Myers & Davis, 2007). This research has implicated sensory cortices, the PAG, inferior colliculus, lateral septum, BNST, as well as the dorsal and ventral striatum to be involved in rodent fear extinction (Herry et al., 2010; Myers & Davis, 2007). Moreover, the amygdala has been frequently suggested to play an important role. However, the findings concerning its involvement are a lot more inconsistent than they are with respect to fear acquisition (Myers & Davis, 2007). A region

that seems to play a special role within fear extinction is the hippocampus (Milad & Quirk, 2012), which has also previously been shown to be important in the acquisition of contextual information during fear conditioning (Phillips & LeDoux, 1992). Within fear extinction, it seems to be relevant for extinction training as well as extinction recall, reinstatement and renewal (Myers & Davis, 2007). This might be related to the fact, that extinction recall is especially dependent on the extinction training context as a retrieval cue (Bouton, Woods, & Pineño, 2004; Vervliet et al., 2013). Another important region within fear extinction seems to be the MPFC, especially its infralimbic region. The infralimbic cortex is considered to be the relevant structure involved in the inhibition of the conditioned CS-US association (Milad & Quirk, 2012; Myers & Davis, 2007; Sotres-Bayon & Quirk, 2010). Correspondingly, extinction recall fails if the VMPFC / infralimbic cortex is damaged (Morgan, Romanski, & LeDoux, 1993; Quirk & Mueller, 2008). When an extinguished CS is presented within the extinction training context, the hippocampus is thought to activate the infralimbic cortex, which in turn activates inhibitory circuits in the basolateral amygdala (Mahanty & Sah, 1998; McDonald, Mascagni, & Guo, 1996; Pare & Smith, 1993). Those subsequently inhibit output neurons in the central amygdala, which leads to the absence of the CR (Graham & Milad, 2011; Quirk & Mueller, 2008).

As for fear acquisition mechanisms, also extinction processes and their neural correlates have been demonstrated to substantially overlap across animals and humans (Milad & Quirk, 2012; Vervliet et al., 2013). Again, the amygdala, hippocampus, and VMPFC are involved (Quirk & Mueller, 2008; Vervliet et al., 2013). During extinction training in humans, the amygdala initially exhibits increased activation, which decreases along with the extinction session, thus mimicking the theoretical construct of within-session extinction (LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998). Furthermore, activity in the OFC is increased during extinction training (Knight, Smith, Cheng, Stein, & Helmstetter, 2004). Upon future confrontations with the CS, the hippocampus signals the VMPFC to activate inhibitory networks in the amygdala that in turn downregulate the centromedial nucleus and thus fear reaction (Greco & Liberzon, 2015; Maren, 2008; Vervliet et al., 2013). Correspondingly, VMPFC (Phelps, Delgado, Nearing, & LeDoux, 2004; Graham & Milad, 2011) as well as hippocampal activity (Knight et al., 2004) were shown to be increased during extinction recall, as it was demonstrated for rodents (Milad, Wright, et al., 2007). Unfortunately, anxiety disorder patients seem to be characterized by impaired fear extinction (Duits et al., 2015).

2.1.5 The treatment of anxiety disorders via behavioral exposure

2.1.5.1 Cognitive Behavioral Therapy

The basic theoretical and neuroscientific findings on fear extinction in animals, humans as well as pathological anxiety were translated by Craske (see Craske et al., 2008; Craske, Liao, Brown, & Vervliet, 2012; Craske et al., 2014) to the level of exposure treatment and subsequently informed modern psychotherapeutic manuals for the treatment of anxiety disorders. Craske et al. (2008) developed the so-called inhibitory model of fear extinction (Sewart & Craske, 2020), which was based on the findings of Bouton (1993), Miller & Matzel (1988) and Wagner (1981). They proposed inhibitory learning to be central to extinction even though also other mechanisms like habituation come into play (Myers & Davis, 2007).

As the different anxiety disorders share various similarities regarding etiology, maintenance, and neurobiology (Barlow, Sauer-Zavala, Carl, Bullis, & Ellard, 2014; Cisler, Olatunji, Feldner, & Forsyth, 2010; Rosellini, Boettcher, Brown, & Barlow, 2015), also their treatment is similar (Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012; Hofmann & Smits, 2008; Smits, Otto, Powers, & Baird, 2019). The central goal is to inhibit the pathological CS-US association via extinction and inhibitory learning respectively. Therefore, the first step within CBT treatment of anxiety disorders is to bring the CS-US associations to mind. They find expression in specific concerns (Beck & Haigh, 2014; Clark & Beck, 2010; Craske et al., 2014) like ‘the spider (CS) is going to bite (US) me’ or ‘I am going to die from a heart attack (US) when being alone at home (CS)’. Direct verification or disconfirmation of those concerns or the associated intensity is possible during in-vivo exposure where patients are instructed to seek real situations or places that allow for a valid examination of their concerns. Meanwhile, omitting safety or avoidance behavior (e.g. drinking water to avoid fainting, sitting close to the door to be able to exit fast) is essential, as it would prevent extinction due to the absence of the US being associated with the presence of the avoidance behavior. Exposure treatment is the core element of CBT in anxiety disorders, as it represents the implementation of fear extinction via inhibitory learning within the therapeutic process (Craske et al., 2017; Craske et al., 2014). Therefore, it constitutes the result of a successful translational process from animal models to the treatment of mental disorders in humans.

2.1.5.2 Neural changes following CBT in anxiety disorders

Hauner, Mineka, Voss, & Paller (2012) investigated neurofunctional changes due to CBT in specific phobia and found PFC activity to increase from pre- to post-treatment whereas amygdala, insula and cingulate activation decreased after exposure treatment. This is in line with the dual-process model by Barrett, Tugade, & Engle (2004), which has been adapted for emotion regulation and anxiety (Etkin, 2009; Ochsner & Gross, 2005). Dual process models are frequent within psychology as their central assumption is the determination of behavior via the interplay of automatic and controlled processing (Barrett et al., 2004). Those models can be illustrated via the metaphor of a traditional balance with two pans: once regulatory influence decreases, automatic processing increases and vice versa. Applied to anxiety disorders it proposes a hyperactivation of the fear network, which is accompanied by reduced regulatory control via frontal structures (Marwood, Wise, Perkins, & Cleare, 2018; Messina, Sambin, Beschoner, & Viviani, 2016). The applicability of the model to anxiety disorders is supported by the findings on their neural correlates (Duval et al., 2015; Etkin, 2009; Shin & Liberzon, 2010). Furthermore, this is supported by rodent studies of Quirk and Gehlert (2003) and Paré, Quirk and Ledoux (2004) who found the VMPFC to inhibit the amygdala via GABA-ergic interneurons.

As CBT is supposed to enhance regulatory control, it should also lead to an increase of activation within frontal structures (Etkin, 2009; O'Toole, Mennin, Hougaard, Zachariae, & Rosenberg, 2015). However, the results are inconsistent concerning this hypothesis (Linden, 2008; Messina et al., 2016; see e.g. Paquette et al., 2003 for specific phobias). These inconsistencies have been found across the whole group of anxiety disorders: involvement of frontal structures has been observed frequently. However, the direction of change in brain activation due to CBT treatment varies across studies (Marwood et al., 2018). For example, in PD, activation of the left IFG in response to the CS+ was found to be reduced after treatment (Kircher et al., 2013). This likely indicates a reduced need for regulatory effort after treatment and points to hyperactive frontal regions prior to treatment in terms of a compensatory response to the hyperactive fear-related structures. Similarly, an increase in DLPFC activity due to CBT treatment could not be confirmed by the meta-analysis of Messina, Sambin, Palmieri and Viviani (2013). However, the DMPFC seems to be modulated by CBT for affective disorders (Messina et al., 2013). The results of Klahn et al. (2017) regarding the comparison of PD and specific phobia suggest the involvement of the PFC to be dependent on the temporal aspects of the threat stimulus that is the leading cause of anxiety states in the respective disorder. In PD, sustained

fear was accompanied by a hyperactive VMPFC whereas this was not true for specific phobia and the related phasic fear responses.

Taken together, the dual process model fails to provide a comprehensive explanation for the neural changes induced by CBT in anxiety disorders. It seems to be too simple as it neglects e.g. compensatory mechanisms. This thesis does not aim to examine this problem further or to propose potential solutions. However, it is important to keep those differing results in mind when setting up hypotheses regarding potential moderators of treatment outcome.

2.1.5.3 Virtual Reality Exposure Treatment

The term virtual reality (VR) refers to "the use of computer modeling and simulation that enables a person to interact with an artificial three-dimensional (3-D) visual or other sensory environment" (Lowood, 2011). First VR applications emerged during the 1950's and 60's and developed rapidly along with technological advances (Maples-Keller, Bunnell, Kim, & Rothbaum, 2017; Riener & Harders, 2012).

Due to in vivo exposure requesting the therapist and patient to actually seek the feared situations in real life, it is often associated with a heightened expenditure of time and money. Especially the treatment of flight phobia is highly cost-intensive. Facing this problem, attention of CBT therapists was attracted towards VR technology as it enables the comparatively economic simulation of realistic 3-D environments as an alternative to in vivo exposure (Maples-Keller et al., 2017; Mühlberger, Alpers, & Pauli, 2009). It furthermore offers the opportunity to apply exposure stimuli in a highly standardized manner thus supporting comparability and reproducibility within scientific settings (Botella, Fernández-Álvarez, Guillén, García-Palacios, & Baños, 2017). Due to those advantages, VR applications for exposure treatment become more and more popular.

The advancement of VR within CBT is further supported by the promising results on its effectivity compared to in vivo exposure (Wechsler, Kümpers, & Mühlberger, 2019). Virtual reality exposure treatment (VRET) is equally effective in the treatment of anxiety disorders like specific phobia, SAD or PD (Bouchard et al., 2017; Carl et al., 2019; Powers & Emmelkamp, 2008; Valmaggia, Latif, Kempton, & Rus-Calafell, 2016). The achieved results are also generalizable to the patients' real life (Morina, Ijntema, Meyerbröker, & Emmelkamp, 2015; Opriş et al., 2012). Moreover, effectivity is enhanced when more sessions are conducted thus mirror-

ing another characteristic of traditional in vivo CBT (Powers & Emmelkamp, 2008). Psychotherapy research on VRET has also shown that drop-out rates as well as long-term stability are comparable to treatment as usual, too (Opriş et al., 2012). Furthermore, due to the facilitated access to multiple contexts within VRET, return of fear (RoF) is reduced among spider phobia patients (Shiban, Schelhorn, Pauli, & Mühlberger, 2015). This likely indicates an advantage of VRET in terms of generalizability of inhibitory learning.

To summarize, VR has proven to be a useful tool in the treatment of anxiety disorders which resulted in the receipt of VRET into treatment guidelines (Bandelow, Lichte, Rudolf, Wiltink, & Beutel, 2014; Bandelow, Lichte, Rudolf, Wiltink, & Beutel, 2015). It also bears potential to further improve treatment as it facilitates standardized research on the mechanisms of action that are involved in extinction and inhibitory learning (Botella et al., 2017). Encouraged by the positive results with respect to the treatment of anxiety disorders, VR treatment has even been adapted to the treatment of delusions in psychosis where it proved to be highly effective as well (Freeman et al., 2016). However, regardless of the overwhelming results and promising approaches, VRET did not manage to improve rates of treatment responders in anxiety disorders (Opriş et al., 2012).

2.2 Efficacy and moderators of exposure-based treatments

Exposure-based CBT proved to be a powerful approach for treating anxiety disorders. Therefore, it is considered a first-line treatment (Carpenter et al., 2018; Hofmann et al., 2012). According to the German S3 AWMF guideline (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften) on the treatment of anxiety disorders (Bandelow, Lichte, et al., 2014), CBT has been assigned the highest level of evidence (Ia) and the highest recommendation level (A) throughout all different anxiety disorders. Exposure-based CBT shall be offered to patients suffering from anxiety disorders. In PD/AG and SAD a combination of pharmacological and psychotherapeutic treatment with CBT is recommended. With respect to specific phobia, present studies are not sufficient to proof the efficacy of a pharmacological treatment, thus resulting in CBT to be the only recommended treatment (Bandelow, Lichte, et al., 2014; Carpenter et al., 2018).

Even though exposure-based CBT is considered the “gold standard” form of psychotherapy for anxiety disorders (Craske et al., 2017; Hofmann et al., 2012; Hofmann & Smits,

2008), a substantial proportion of patients (ca. 50%; Loerinc et al., 2015) do not respond in a clinically significant manner. Regardless of the development of new approaches like VRET, there is still plenty of room for improvement of response rates (Loerinc et al., 2015; Opriş et al., 2012; Taylor, Abramowitz, & McKay, 2012). The parable of the sower highlights the dependency of the crops on the soil where the seed is sown. Transferred to the treatment of anxiety disorders, CBT outcome might depend on pre-treatment patient characteristics, which represent a more or less fruitful soil for exposure to act. The following paragraphs should review the existing knowledge on such moderating pre-treatment factors. Although a variety of patient- and therapist-factors as well as their interaction will determine the success of a psychotherapy, we here focus on those variables that can be gathered easily as well as reliably prior to treatment: patient characteristics.

With respect to patient factors, one has to consider pathology-related, environment- and culture-related factors as well as treatment non-adherence or non-compliance (Bystritsky, 2006; Taylor et al., 2012). Regarding anxiety disorders, treatment-incompatible motivational stages (Prochaska, DiClemente, & Norcross, 1992) prior to and during treatment can impair response rates (Böhnlein et al., 2020) as e.g. therapeutic homework might not be conducted (Kazantzis, Whittington, & Dattilio, 2010), overcoming avoidance is not possible or exposure is rejected (Pittig et al., 2020). Furthermore, high self-efficacy prior to treatment seems to be beneficial (Böhnlein et al., 2020). With respect to cultural factors, reduced suffering from SAD symptoms within Asian cultures or culture-specific expressions of certain disorders like *Taijin kyofusho* (= Japanese expression of SAD) are discussed as influencing treatment response as well (Hofmann, Anu Asnaani, & Hinton, 2010; Le Meyer, Zane, Cho, & Takeuchi, 2009). Moreover, environmental factors like acute (severe) stressors e.g. death of a relative, childhood stressors e.g. trauma or maltreatment, or long-term persistent stressors e.g. unemployment or low socio-economic status have been related to worse treatment response (Bystritsky, 2006; Deckert & Erhardt, 2019). Additionally, patients from families with high expressed emotions seem to exhibit poorer treatment outcome (Taylor et al., 2012). Within the meta-analysis of Schneider, Arch and Wolitzky-Taylor (2015), demographic factors like age and sex failed as predictors of CBT outcome in anxiety disorders.

Finally, pathology-related factors exert an important influence on treatment response. Of those, heightened severity at baseline was shown to affect treatment outcome negatively (Liber et al., 2010; Taylor et al., 2012). Correspondingly, high levels of trait anxiety were shown to have a detrimental effect (Böhnlein et al., 2020). Certain diagnoses are associated with

heightened severity and thus worse treatment outcome on average. As an example, anxiety symptomatology and emotional burden are usually stronger in SAD compared to specific phobia, which results in lower response rates (Deckert & Erhardt, 2019). However, severity of symptomatology has been shown to affect treatment outcome within one nosological entity as well (Taylor et al., 2012). Nevertheless, the meta-analysis of Schneider et al. (2015) questioned the role of severity with respect to treatment outcome as findings were inconclusive. The same meta-analysis found moderate anxiety sensitivity levels to be beneficial for CBT outcome. However, this might also relate to the dependency of severity and motivation for exposure.

Another important moderating pathology-related patient factor, which is also related to severity is comorbidity (Olatunji, Cisler, & Tolin, 2010). However, findings are mixed and seem to depend on the present comorbid disorder (Olatunji et al., 2010). Overall, results point to non-anxiety comorbidity to be related to worse treatment outcome (Liber et al., 2010). In contrast, comorbidity - especially with other anxiety disorders (Ollendick, Öst, Reuterskiöld, & Costa, 2010) – does not seem to impede treatment of childhood anxiety disorders (Kendall, Brady, & Verduin, 2001). This is supported by findings of Ryan, Strege, Oar and Ollendick (2017), who observed no limitations in reduction of childhood phobia severity by the presence of comorbid GAD or SAD. Moreover, generalization effects across comorbid specific phobias have been observed (Ollendick et al., 2010). Non-pathological personality traits like conscientiousness, neuroticism and openness did reach inconclusive or non-significant results (Schneider et al., 2015). However, comorbid personality disorders seem to impede CBT outcome in anxiety disorders (Schneider et al., 2015). This was demonstrated e.g. for avoidant personality disorder in SAD (Hofmann, 2000). In contrast, comorbid substance-use disorder did not diminish treatment outcome of anxiety disorders substantially (McEvoy & Shand, 2008). Similar results have been observed for depressive comorbidity (Allen et al., 2010; Lueken et al., 2015; Schneider et al., 2015). However, Walczak, Ollendick, Ryan and Esbjørn (2018) found meta-analytic evidence for pronounced detrimental effects on treatment outcome in SAD with comorbid mood disorders. Deckert and Erhardt (2019) reported corresponding results. Overall, the findings with respect to comorbidity highlight the differential impact varying comorbidities might have on treatment outcome. In general, comorbidity does seem to moderate outcomes (Brown, Antony, & Barlow, 1995; Walczak et al., 2018). Fortunately, comorbid disorders usually improve along with anxiety disorder improvement (Brown et al., 1995; Walczak et al., 2018).

Within their meta-analysis, Schneider et al. (2015) only found few studies addressing baseline neurobiological measures. None of the tested genetic markers was significant. Roberts et al. (2017) and Coleman et al. (2016) reported similar findings within their genome-wide association studies. Instead, Lueken et al. (2016) demonstrated the serotonin transporter linked polymorphic region (5-HTTLPR) rs25531 variant as well as cardiovascular flexibility as moderators of treatment outcome. S-allele carriers of the 5-HTTLPR gene seem to be susceptible to RoF and thus poorer treatment outcome (Wannemüller, Moser, Kumsta, Jöhren, & Margraf, 2018). However, this contradicts findings from Eley et al. (2012) who found improved CBT outcomes in those patients. Further serotonin-related gene variants like monoamine-oxidase A (MAO-A) are studied and yielded meta-analytic support as well (Lueken et al., 2016). For an overview of (epi)genetic response markers see e.g. Lueken & Hahn (2020). Apart from genetics, Merz et al. (2011) also proposed sex hormones to alter extinction and thus treatment outcome.

Neurofunctional studies directly assessing pre-treatment neural signatures in anxiety disorders are accumulating within the last years (Lueken & Hahn, 2016, 2020; Maron & Nutt, 2015; Shin, Davis, VanElzakker, Dahlgren, & Dubois, 2013) and provide first insights in potential moderators of treatment outcome in anxiety disorders (Lueken et al., 2016; Marwood et al., 2018; Santos, Carvalho, Van Ameringen, Nardi, & Freire, 2019). The meta-analysis of Lueken et al. (2016) revealed the ACC and its coupling with the amygdala as a potential predictive biomarker for response in anxiety disorders. Furthermore, they reported some preliminary evidence for the hippocampus as well as the frontal lobe as additional structures with potential predictive value. The meta-analysis of Marwood et al. (2018) also investigated potential predictors of response to psychotherapy in anxiety disorders and again found the ACC to be the brain region exhibiting the most consistent results (see also Chakrabarty, Ogrodniczuk, & Hadjipavlou, 2016). Decreased activity within the ACC after treatment was significantly associated with more symptomatic improvement. Furthermore, this was true for the bilateral inferior frontal gyrus (IFG) and left insula. On the other hand, increased activity of the cuneus and precuneus prior to treatment was predictive for better treatment outcome, too. Recently, Santos et al. (2019) reviewed the current state of research on predictors of treatment outcome in anxiety disorders again. They found the amygdala, right cuneus, superior occipital gyrus, insula, ACC, right angular gyrus, bilateral DLPFC, DMPFC, right hippocampus, left uncus, left transverse temporal gyrus, left supramarginal gyrus, left precentral gyrus, MTG, left superior frontal gyrus (SFG), and right substantia nigra to be indicative of response to CBT in SAD. In PD/AG and

GAD the ACC, hippocampus, insula, DLPFC, amygdala, and left IFG were found to be indicative for treatment response (Santos et al., 2019). Furthermore, baseline emotion regulation related activity (i.e. less pretreatment DLPFC recruitment) predicted treatment outcome in SAD (Klumpp et al., 2017).

In summary, previous studies on moderators of treatment outcome in anxiety disorders highlight the relevance emotion regulation, which seems to change via exposure-based CBT as indicated by the consistent recital of frontal/regulative structures like the ACC, IFG, DLPFC and DMPFC across studies. On the other hand, regions related to higher order visual perception and attention like the cuneus, precuneus or angular gyrus that have yet received less attention with respect to anxiety disorders seem to play an important role when it comes to treatment outcome (Doehrmann et al., 2013; Santos et al., 2019).

2.3 Main research questions

The identification of moderators of fear extinction might aid in bridging the large response gap among anxiety disorder patients as they would provide starting points for personalized, modified and add-on treatments. Research on the neural correlates of fear conditioning, extinction and anxiety disorders has led to the development of today's effective exposure treatment. Accordingly, neural moderators of treatment outcome might be especially promising with respect to the improvement of response rates. However, comorbidity has only rarely been studied with respect to its (neural) implications for treatment outcome. Furthermore, pre-treatment resting-state functional connectivity signatures that might moderate treatment outcome in anxiety disorders are largely unknown. Therefore, this thesis aimed at investigating two major research questions: first, does secondary SAD influence the neural substrates and treatment outcome of primary PD/AG? Second, are there differences in pre-treatment resting-state functional connectivity signatures between spider phobia patients responding to exposure based-treatment and those who do not respond?

3 The moderating impact of comorbidity on treatment outcome among anxiety disorders

Chapter 3 is based on the manuscript of Seeger et al. (2019) entitled "Clinical and neurofunctional substrates of cognitive behavioral therapy on secondary social anxiety disorder in primary panic disorder: a longitudinal fMRI study", which was published in *Psychotherapy & Psychosomatics*. A permission to reproduce text, figures and data within this thesis has been obtained by Karger AG, Medical and Scientific Publishers, Basel, Switzerland and can be found within Appendix A.

3.1 Theoretical background

Clinicians frequently treat patients suffering from more than one mental disorder (Wittchen et al., 2011). As they have to decide which disorder to treat first, it is of high clinical relevance to know how comorbidity influences the symptomatology of the primary disorder and whether the treatment of one disorder also affects the course of the other. Moreover, knowledge on generalization effects or even comorbidity-associated obstacles during treatment should guide the clinician´s decision to achieve optimal treatment outcome (Seeger et al., 2019).

As mentioned above, anxiety disorders belong to the most frequent mental disorders and exhibit high comorbidity ratios (Wittchen et al., 2011). Especially patients with PD and AG often suffer from other mental disorders (DSM-IV-TR, 2000; DSM-V, 2013; Goodwin et al., 2005). Among these, SAD represents a frequent comorbidity (Kessler et al., 2006). While exposure-based CBT is an effective first-line treatment for both primary PD/AG and SAD (Bandelow, Seidler-Brandler, Becker, Wedekind, & Rüther, 2007; Bandelow, Wiltink, et al., 2014; Carpenter et al., 2018), it is largely unknown whether CBT for PD/AG may generalize to SAD or if comorbid SAD may on the contrary impede the treatment of primary PD/AG and thus diminish treatment outcome.

Neuroimaging research is increasingly elucidating the neural substrates of anxiety disorders and the neural mechanisms by which CBT acts upon the brain (Barsaglini, Sartori, Benetti, Pettersson-Yeo, & Mechelli, 2014; Kircher et al., 2013; Lueken & Hahn, 2016; Messina et al., 2013). In line with these similarities in how PD/AG and SAD are generally treated (e.g. CBT), both disorders exhibit substantial overlap on a neurofunctional level within

the brain's defensive system (McNaughton & Corr, 2004; Mobbs et al., 2007). Meta-analytic evidence on SAD (Brühl, Delsignore, Komossa & Weidt, 2014; Kim & Yoon, 2018) implicates a network consisting of the bilateral amygdalae, the BNST, the parahippocampal gyrus, the right insula, the ACC, the left DLPFC, and MPFC, but also bilateral occipitotemporal brain regions during specific tasks as well as at rest. In PD, a network also encompassing the bilateral amygdalae, insulae, BNST, ACC, and other frontal regions, but also lower brain stem regions including the PAG has been described during resting state measurement and fMRI tasks (Dresler et al., 2013; Lueken et al., 2014). When subtracting the overlapping defensive network structures, the main differences between PD/AG and SAD refer to the brain stem (incl. PAG) as well as occipitotemporal and parietal regions related to the ventral object recognition pathway (Gilbert, 2013) and the salience network (Kim & Yoon, 2018). Those networks might be especially relevant in SAD due to the high relevance of detecting social cues (faces; Doehrmann et al., 2013). Neuroimaging studies to date are however limited by the fact that comorbidity is rarely reported or controlled for. Hence, it is unclear to which extent the observed common and distinct neural signatures can be explained by confounding comorbidity issues between PD/AG and SAD and how these neural and behavioral correlates are modulated by CBT and affect treatment outcome.

Fear conditioning is considered to be involved in the pathogenesis of anxiety disorders and serves as experimental model for their development, maintenance and treatment via exposure therapy (Craske et al., 2008; Craske et al., 2014; Duits et al., 2015; Vervliet et al., 2013). By triggering behavioral and neural components of defensive responses, fear conditioning enables the organism to avoid future threats in that important information (CS, such as agoraphobic or socially relevant situations) signaling a potential threat (US, such as a panic attack or social defeat) elicits defensive reactions (CR). On a neural level, fear conditioning involves multiple areas associated with defensive responding such as the (pre-) motor cortex, MPFC/ACC, anterior insula, amygdala, hippocampus, and thalamus (Fullana et al., 2016; Sehlmeyer et al., 2009) which have also been partly identified as pathophysiological correlates of both PD/AG (Dresler et al., 2013; Lueken et al., 2014) and SAD (Kim & Yoon, 2018). The overlap in these neural substrates may be due to shared pathogenic pathways that are based on fear conditioning.

The aim of this analysis was to investigate how secondary SAD affects clinical and neurofunctional response parameters in primary PD/AG patients that are treated via exposure-based CBT specifically tailored to target primary PD/AG. We hypothesized that in

PD/AG+SAD patients the effects of CBT targeting PD/AG will generalize and improve SAD symptoms thus leading to a similar treatment outcome. Furthermore, we expected to detect a specific neural signature of comorbid SAD at baseline as represented by enhanced activation in the ventral object recognition pathway within the temporal lobe. Primary SAD patients have been shown to exhibit enhanced activation within this pathway during the detection of visual stimuli (Brühl, Delsignore, Komossa, & Weidt, 2014; Etkin & Wager, 2007). Finally, and in line with our hypothesis on generalization effects of CBT, we expected this specific neural signature in PD/AG+SAD patients to attenuate to the level of PD/AG-SAD patients following treatment.

3.2 Methods

3.2.1 Participants

We here present a secondary analysis of data originally collected by the German research network "Panic-Net", a randomized controlled clinical trial on exposure-based CBT in PD/AG (Gloster et al., 2011). Eight centers throughout Germany participated in the clinical trial (Aachen, Berlin-Adlershof, Berlin-Charité, Bremen, Dresden, Greifswald, Münster, Würzburg). Four centers (Aachen, Berlin-Charité, Dresden, Münster) additionally conducted an fMRI study. From the entire sample of 369 patients enrolled in the clinical trial, 242 completer datasets were available for the present analysis. For details regarding the study protocol (including a CONSORT flowchart), in- and exclusion criteria as well as measures of fMRI data quality control see the corresponding publications (Gloster et al., 2011; Kircher et al., 2013). Only currently medication-free patients (i.e. 4-week washout period) with a primary diagnosis of PD/AG according to DSM-IV-TR criteria were included. Diagnostic criteria were assessed by means of a standardized interview (Composite International Diagnostic Interview; CAPI-WHO-CIDI; DIAX-CIDI version; Wittchen & Pfister, 1997) validated by clinical experts, a Hamilton Anxiety Scale Score (SIGH-A; Shear et al., 2001) ≥ 18 and a Clinical Global Impression Score (CGI; Guy, 1976) ≥ 4. Patients were aged between 18 and 65 years. Clinically significant suicidal intent, inability to comply with the study schedule, meeting diagnostic criteria for any psychotic or borderline personality disorder, bipolar disorder or current alcohol dependence, medical conditions explaining anxiety symptoms and MRI-related contraindications led to exclusion. Patients meeting the criteria for other current comorbid diagnoses, including major depression, dysthymia and other anxiety disorders were included, as long as they were not the

primary diagnosis. Therefore, the sample can be considered as representative of patients seen in clinical practice. 194 patients were recruited for the trial and 89 of these patients consented to participate in the fMRI study. 42 quality-controlled data sets including pre- and posttreatment fMRI assessments and clinical outcome data were available (for details on data quality control in this multicenter study please refer to Kircher et al., 2013). This study has been conducted in accordance with the Declaration of Helsinki and has been approved by the ethics committees of all eight participating centers. The participants provided written informed consent.

For the present analysis, PD/AG patients were grouped according to the presence of comorbid SAD (DSM-IV-TR 12-month diagnosis of SAD). In the clinical sample 100 patients (41.3 %) exhibited a comorbid SAD (PD/AG+SAD), while in the fMRI subsample 14 patients (33.3 %) were in the PD/AG+SAD group. Sociodemographic and clinical characteristics between groups were tested using $\chi 2$- and t-tests. Within (baseline vs. after therapy) and between group (PD/AG+SAD vs. PD/AG-SAD) differences in treatment outcomes were analysed using linear regressions while adjusting for baseline values. Two robust alternatives were fitted to consider potential violations in model assumptions: robust estimation of standard errors (with the sandwich matrix, accounting for non-normal distributions and different variances in residuals) and robust linear regression (accounting also for observations that might otherwise have a strong influence on results; Field & Wilcox, 2017). The significance threshold was set to two-sided alpha = .05. Clinical data were analysed using Stata, version 14.2 (StataCorp., 2016) and SPSS, version 24 (IBM, Armonk, N.Y.).

3.2.2 Exposure-based cognitive behavioral therapy

All patients (PD/AG+SAD and PD/AG-SAD) received the same manualized 12-session CBT treatment, which was conducted by trained therapists targeting the primary diagnosis of PD/AG. The protocol was carried out over six weeks and was followed by two booster sessions (Gloster et al., 2011). The manualized therapy comprised psychoeducation, functional analysis of symptoms and related coping behaviors, rationale for exposure, interoceptive exposure, standardized exposure in situ (forest, shopping mall, bus), anticipatory anxiety, individualized in situ exposure (e.g. the patients' most feared situation) and relapse prevention. The aim of the original trial was to compare the effects of therapist-guided exposure vs. patient-guided exposure. Both treatment conditions proved to be highly effective (Gloster et al., 2011) with some benefits for the therapist-guided treatment arm targeting agoraphobic behaviors. As patients

with and without comorbid SAD were equally distributed across treatment arms (Table 1), they were merged for the current analysis.

3.2.3 Clinical assessments

The Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A; total score; Shear et al., 2001), was used as the primary outcome measure. Clinical response was defined as a reduction of at least 50 % from baseline to post-treatment scores. The Brief Symptom Inventory subscale Interpersonal Sensitivity (BSI; Derogatis & Melisaratos, 1983; Franke, 2000) served as a proxy self-report measure of social anxiety symptomatology. It has been shown to correlate significantly with widely used measures of social anxiety like the Social Interaction Anxiety Scale (SIAS; r = .72) or the Social Phobia Scale (SPS; r = .63; Geisheim et al., 2002).

3.2.4 Fear conditioning task

As neurofunctional probe of interest we applied a previously validated (Lueken et al., 2014; Reinhardt et al., 2010) differential fear conditioning task using colored geometric stimuli as CSs (presentation time: 2000 ms with a variable inter-trial interval (ITI) of 4.785 to 7.250 sec). An aversive white noise (100 ms) represented the US (50 % partial reinforcement rate, CS counterbalanced across subjects; total task duration: approx. 17 min). While fear learning is induced by the reinforced CS+, the CS- (which is never followed by the US) acquires characteristics of a safety signal. The task comprised three phases (familiarization (F) with 16 trials; acquisition (A) with 32 trials and extinction (E) with 16 trials of each CS). During the acquisition phase, we only analysed those trials in which no US was delivered (CS+unpaired). After each phase the patients were asked to rate valence and arousal of the CSs on a five-point Likert-type scale (1, “very unpleasant” / “not arousing” to 5, “very pleasant” / “very arousing”) using the self-assessment Manikin (SAM; Bradley & Lang, 1994). For results concerning the behavioral ratings as indicators of contingency knowledge see (Kircher et al., 2013). For stimulus presentation we used Presentation 11 (Neurobehavioral Systems; www.neurobs.com) accompanied by MR-compatible LCD goggles (VisuaStimDigital, Resonance Technology Inc., Northridge, CA) and standard headphones.

3.2.5 fMRI data acquisition and analysis

As described previously (Kircher et al., 2013), MRI images were acquired using 3-T Philips Achieva (Aachen, Münster), 3-T Siemens Trio (Dresden), and 3-T General Electric Healthcare (Berlin) scanners. A total of 505 axial functional images (matrix = 64 x 64; 30 slices interleaved; field of view = 230; voxel size = 3.6 x 3.6 x 3.8 mm; TE = 30 ms; TR = 2 seconds), covering the whole brain and positioned parallel to the intercommissural line (anterior commissure-posterior commissure) were recorded. The first five volumes were discarded to reduce T1 saturation effects. All images were preprocessed using SPM5 (www.fil.ion.ucl.ac.uk) implemented in MATLAB, version 7.1 (MathWorks, Natick, Mass.), applying a high-pass filter (cut-off period, 128 seconds) to remove low-frequency fluctuations in the blood-oxygen-level-dependent (BOLD) signal. After slice time correction, functional images were temporally and spatially aligned and normalized into the stereotactic Montreal Neurological Institute template (MNI, 2 x 2 x 2 mm). An iterative smoothness equalization procedure (Friedman, Glover, & Consortium, 2006) was performed using a 12-mm full width at half-maximum (FWHM) Gaussian isotropic kernel (comparable to a kernel of 8 mm in a standard smoothing procedure). At first level, realignment parameters were included as regressors of no interest. The BOLD response was modelled for each event type (CS+ paired, CS+ unpaired, CS- and US) and phase (familiarization, acquisition, and extinction) convolved with the canonical hemodynamic response function used in SPM5 within the framework of the general linear model (GLM). Each phase was divided by half into an early and a late part to account for temporal aspects and habituation, resulting in 16 regressors (familiarization: early CS+, late CS+; early CS-, late CS-; US; acquisition: early CS-, late CS-, early CS presented with the US (CS+paired); early CS+ without US (CS+unpaired), late CS+paired; late CS+unpaired; US; extinction: early CS-, late CS-; early CS+, late CS+; behavioral assessment). Parameter estimates (beta values) and t-statistic images were calculated for each subject.

The group analysis was performed in SPM8 (www.fil.ion.ucl.ac.uk) implemented in MATLAB, R2012b (MathWorks, Natick, Mass.), by including contrast images into a flexible factorial analysis where subjects are treated as random variables. As previously (Kircher et al., 2013; Lueken et al., 2013; Lueken et al., 2014), we included an fMRI center variable to account for scanner differences between sites. Age, Anxiety Sensitivity Index (ASI; Alpers & Pauli, 2001), CGI and Beck Depression Inventory (BDI-II; Hautzinger, Keller, & Kühner, 2006) scores were additionally entered as covariates to control for group differences between

PD/AG+/-SAD (see supplemental Table S1). Two separate models were set up to test for baseline differences only (model 1: including data only from prior to therapy) and longitudinal data from baseline to post (model 2). In the first model, F-contrasts were computed separately for acquisition and extinction phases for the main effect of group and group x CS interaction; for the second model, the group x time interaction and group x time x CS interaction, followed by post-hoc t-contrasts to specify the direction of the effect (PD/AG+SAD > PD/AG-SAD, PD/AG-SAD > PD/AG+SAD, PD/AG+SAD (CS+ > CS-) > PD/AG-SAD (CS+ > CS-), PD/AG-SAD (CS+ > CS-) > PD/AG+SAD (CS+ > CS-), PD/AG+SAD (T1 > T2) > PD/AG-SAD (T1 > T2), PD/AG-SAD (T1 > T2 > PD/AG+SAD (T1 > T2), PD/AG+SAD: T1 > T2 (CS+ > CS-) > PD/AG-SAD: T1 > T2 (CS+ > CS-), PD/AG-SAD: T1 > T2 (CS+ > CS-) > PD/AG+SAD: T1 > T2 (CS+ > CS-)). As in previous studies (Kircher et al., 2013), a Monte Carlo simulation of the brain volume was conducted to establish an appropriate voxel contiguity threshold (Slotnick, Moo, Segal, & Hart, 2003). Assuming an individual voxel type I error at $p < 0.005$, a cluster extent of 142 contiguous resampled voxels was indicated as sufficient to correct for multiple voxel comparisons at $P < 0.05$. Since this correction algorithm could bias findings toward larger brain regions, a region-of-interest (ROI) analysis of the amygdala was conducted using the Automated anatomical labeling atlas (AAL; Tzourio-Mazoyer et al., 2002; $p < 0.05$, familywise-error corrected based on a clusterforming threshold of $p < 0.001$). Monte-Carlo simulations, like the one established for the "Panic-Net" studies, have recently been criticized as they may facilitate false-positive results (Eklund, Nichols, & Knutsson, 2016). Due to reasons of comparability between all "Panic-Net" studies we decided to maintain the correction method for multiple comparisons for the present investigation. With respect to Eklund et al., (2016), our results have to be treated as preliminary results and need further replication in a larger sample. Beta values were extracted using a 5mm sphere for visualisation and used for repeated measures analysis of variance (ANOVA) as well as post-hoc t-contrasts from the corresponding main and interaction effects. In case of a violation of the sphericity assumption Greenhouse-Geisser corrected values were reported.

3.3 Results

3.3.1 Clinical effects

Sample characteristics of the clinical completer sample ($n = 242$) and the fMRI sample are given in Table 1 and Table 2, respectively.

In the clinical completer sample (Table 3) as well as in the fMRI sample (Table 4), both groups showed a significant reduction on all primary outcomes as well as on the BSI interpersonal sensitivity subscale. Of note, the effect size of symptom reduction did not differ as a function of comorbidity, indicating that all patients benefited equally well from exposure-based CBT for primary PD/AG. In addition, CBT was able to effectively reduce symptoms of social anxiety to the level of PD/AG-SAD in PD/AG+SAD patients (Figure 1; BSI – interpersonal sensitivity: main effect of time, $F(1,40) = 29.660$, $p < 0.001$, and group*time interaction, $F(1,40) = 11.142$, $p < 0.01$; SIGH-A: main effect of time, $F(1,40) = 113.316$, $p < 0.001$, and group*time interaction, $F(1,40) = 0.006$, $p = 0.938$).

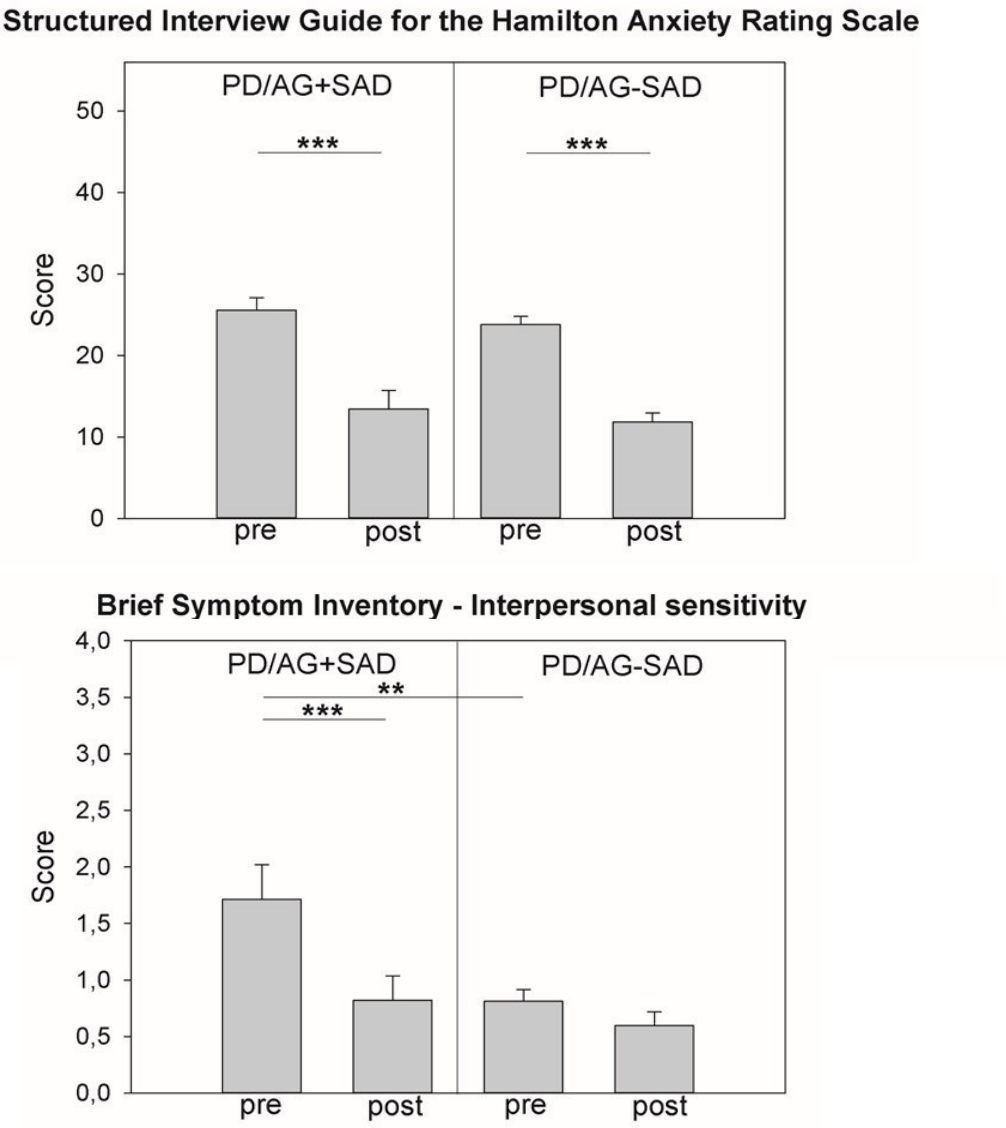


Figure 1. Changes in clinical measures of symptom severity following CBT. Bar graphs show group differences and changes following CBT (pre/post) in the clinical completer sample (n = 242) for the Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A) as the primary outcome and the Brief Symptom Inventory – interpersonal sensitivity subscale (BSI-Sens) as a proxy for symptoms of social anxiety. Error bars indicate the standard error of mean. BSI-Sens: main effect of time, $F(1,40) = 29.660$, $p < 0.001$, and group*time interaction, $F(1,40) = 11.142$, $p < 0.01$; SIGH-A: main effect of time, $F(1,40) = 113.316$, $p < 0.001$, and group*time interaction, $F(1,40) = 0.006$, $p = 0.938$). ** $p < 0.01$; *** $p < 0.001$.

Table 1. Demographic and clinical characteristics of the clinical completer sample. Means (SD), except where noted.

	All patients (n = 242)		PD/AG-SAD (n =142)		PD/AG+SAD (n = 100)		Chi^2 or t (df)	p
Demographic and clinical characteristics								
Female gender [n (%)]	182	(75.21)	108	(76.06)	74	(74.00)	0.133 (1)	0.715
Years of education [n (%)]							4.474 (3)	0.215
8	23	(9.50)	12	(8.45)	11	(11.00)		
10	104	(42.98)	55	(38.73)	49	(49.00)		
12-13	109	(45.04)	72	(50.70)	37	(37.00)		
no formal degree	6	(2.48)	3	(2.11)	3	(3.00)		
Age (years)	35.16	(10.74)	35.70	(10.70)	34.37	(34.37)	0.962 (240)	0.337
Age of onset PD/AG (years)[1]	27.01	(9.85)	27.39	(9.53)	26.50	(10.28)	0.681 (233)	0.497
Age of onset SAD (years)[2]	-	-	-	-	22.61	(10.12)	-	-
Number of patients in therapist-guided treatment arm [n (%)]	129	(53.31)	74	(52.11)	55	(55.00)	0.197 (1)	0.658
Number of treatment responders [n (%)]*	134	(55.37)	82	(57.75)	52	(52.00)	0.784 (1)	0.376
Symptom severity at baseline								
CGI	5.26	(0.71)	5.17	(0.71)	5.39	(0.68)	-2.417 (240)	0.016
BSI – interpersonal sensitivity	1.07	(0.84)	0.92	(0.77)	1.29	(0.90)	-3.350 (240)	0.001
SIGH-A total	24.17	(5.17)	23.75	(5.12)	24.77	(5.21)	-1.508 (240)	0.133
PAS total	27.64	(9.78)	25.67	(9.31)	30.43	(9.80)	-3.826 (240)	< 0.001
ASI total	31.57	(11.30)	29.66	(11.04)	34.27	(11.17)	-3.185 (240)	0.002
BDI II total	16.46	(8.66)	14.88	(8.61)	18.71	(8.26)	-3.464 (240)	0.001

PD/AG+SAD: patients with primary panic disorder and agoraphobia with secondary social anxiety disorder; PD/AG-SAD: patients with primary panic disorder and agoraphobia without secondary social anxiety disorder; CGI: Clinical Global Impressions Scale; BSI: Brief Symptom Inventory; SIGH-A: Structured Interview Guide for the Hamilton Anxiety Rating Scale; PAS: Panic and Agoraphobia Scale; ASI: Anxiety Sensitivity Index; BDI II: Beck Depression Inventory II; [1] available for n = 235 patients (n = 135 in PD/AG-SAD group); [2] available for n = 97 patients; *treatment response was defined as a reduction in SIGH-A scores of at least 50% from baseline to post.

Table 2. Demographic and clinical characteristics of the fMRI sample. Means (SD), except where noted.

	All patients (n = 42)		PD/AG-SAD (n = 28)		PD/AG+SAD (n = 14)		Chi^2 or t (df)	p
Demographic and clinical characteristics								
Female gender [n (%)]	29	(69.05)	20	(71.43)	9	(64.29)	0.223 (1)	0.637
Years of education [n (%)]							7.150 (2)	0.028
8	4	(9.52)	3	(10.71)	1	(7.14)		
10	18	(42.85)	8	(28.57)	10	(71.43)		
12-13	20	(47.62)	17	(60.71)	3	(21.43)		
Age (years)	35.42	(10.17)	37.73	(9.95)	30.79	(9.28)	2.178 (40)	0.035
Comorbid SAD [n(%)]	14	(33.33)	-	-	14	(100.00)	-	-
Age of onset PD/AG (years) [1]	27.16	(10.61)	28.92	(10.29)	23.86	(10.79)	1.461 (38)	0.152
Age of onset SAD (years) [2]	-	-	-	-	22.36	(9.18)	-	-
Number of patients in therapist-guided treatment arm [n (%)]	22	(52.38)	15	(53.57)	7	(50.00)	0.048 (1)	0.827
Number of treatment responders [n (%)]*	25	(59.52)	17	(60.71)	8	(57.41)	0.049 (1)	0.824
Symptom severity at baseline								
CGI	5.36	(0.62)	5.21	(0.63)	5.64	(0.50)	-2.219 (40)	0.032
BSI – interpersonal sensitivity	1.11	(0.90)	0.81	(0.55)	1.71	(1.15)	-3.463 (40)	0.001
SIGH-A total	24.38	(5.41)	23.79	(5.22)	25.57	(5.77)	-1.010 (40)	0.319
PAS total	25.97	(8.69)	24.45	(8.85)	29.02	(7.78)	-1.637 (40)	0.109
ASI total	31.10	(9.37)	28.86	(7.23)	35.57	(11.65)	-2.302 (40)	0.027
BDI II total	17.26	(9.28)	15.35	(7.59)	21.07	(11.34)	-1.994 (40)	0.059

PD/AG+SAD: patients with primary panic disorder and agoraphobia with secondary social anxiety disorder; PD/AG-SAD: patients with primary panic disorder and agoraphobia without secondary social anxiety disorder; CGI: Clinical Global Impressions Scale; BSI: Brief Symptom Inventory; SIGH-A: Structured Interview Guide for the Hamilton Anxiety Rating Scale; PAS: Panic and Agoraphobia Scale; ASI: Anxiety Sensitivity Index; BDI II: Beck Depression Inventory II; [1]available for n = 40 patients; [2]available for n = 11 patients; * treatment response was defined as a reduction in SIGH-A scores of at least 50% from baseline to post.

Table 3. CBT outcomes by baseline social anxiety disorder comorbidity in the clinical completer sample (n = 242).

			Baseline		Post		Effect size*				Effect size difference**		
Outcome	SAD	n	Mean	SD	Mean	SD	point estimate	95% CI		p-value	point estimate	95% CI		p-value
SIGH-A total	no	142	23.75	5.12	11.80	7.09	-2.28	-2.50	-2.05	0.000	*Ref.*			
	yes	99	24.71	5.20	13.53	7.59	-2.13	-2.42	-1.84	0.000	0.24	-0.10	0.58	0.164
CGI total	no	142	5.17	0.71	3.37	1.07	-2.60	-2.86	-2.34	0.000				
	yes	99	5.38	0.68	3.63	1.05	-2.54	-2.85	-2.23	0.000	0.22	-0.16	0.61	0.247
PAS total	no	141	25.63	9.32	12.88	8.55	-1.31	-1.46	-1.15	0.000				
	yes	97	30.57	9.76	16.44	9.25	-1.45	-1.65	-1.25	0.000	0.14	-0.07	0.36	0.191
Number of panic attacks	no	142	2.35	2.28	0.99	1.53	-0.58	-0.74	-0.42	0.000				
	yes	100	2.86	2.43	1.29	1.75	-0.67	-0.88	-0.46	0.000	0.08	-0.09	0.25	0.364
Mobility Inventory	no	126	2.78	0.78	1.77	0.71	-1.21	-1.35	-1.06	0.000				
	yes	89	3.22	0.80	2.19	0.94	-1.22	-1.41	-1.03	0.000	0.20	-0.03	0.42	0.085
BSI – interpersonal sensitivity	no	142	0.92	0.77	0.60	0.70	-0.37	-0.49	-0.25	0.000				
	yes	100	1.29	0.90	0.73	0.78	-0.64	-0.83	-0.44	0.000	-0.06	-0.25	0.12	0.498

CBT: Cognitive behavioral therapy; SIGHA: Structured Interview Guide for the Hamilton Anxiety Rating Scale; CGI: Clinical Global Impressions Scale; PAS: Panic and Agoraphobia Scale; BSI: Brief Symptom Inventory; * Cohens d = post minus baseline difference divided by the standard deviation at baseline of the total sample (n = 369). Confidence intervals and p-values based on linear regression; ** Based on linear regression, adjusted for an outcome's baseline values.

Table 4. CBT outcomes by baseline social anxiety disorder comorbidity in the fMRI sample (n = 42).

			Baseline		Post		Effect size*				Effect size difference**		
Outcome	SAD	n	Mean	SD	Mean	SD	point estimate	95% CI		p-value	point estimate	95% CI	p-value
SIGH-A total	no	28	23.79	5.22	11.82	6.02	-2.28	-2.79	-1.77	0.000			
	yes	14	25.57	5.77	13.43	8.55	-2.31	-3.07	-1.56	0.000	0.13	-0.69 0.96	0.745
CGI total	no	28	5.21	0.63	3.61	1.03	-2.32	-2.94	-1.71	0.000			
	yes	14	5.64	0.50	3.43	1.09	-3.20	-4.14	-2.26	0.000	-0.46	-1.52 0.60	0.388
PAS total	no	28	24.45	8.85	13.62	8.31	-1.11	-1.42	-0.81	0.000			
	yes	14	29.02	7.78	14.62	9.37	-1.48	-1.79	-1.16	0.000	-0.21	-0.67 0.24	0.349
Number of panic attacks	no	28	2.82	2.21	1.36	1.87	-0.62	-1.00	-0.25	0.002			
	yes	14	2.57	1.45	1.14	1.75	-0.61	-1.24	0.02	0.057	-0.07	-0.58 0.44	0.788
Mobility Inventory	no	25	2.48	0.92	1.65	0.62	-0.99	-1.35	-0.63	0.000			
	yes	14	3.13	0.41	2.06	0.78	-1.28	-1.75	-0.80	0.000	0.13	-0.38 0.64	0.615
BSI – interpersonal sensitivity	no	28	0.81	0.55	0.60	0.64	-0.25	-0.47	-0.02	0.031			
	yes	14	1.71	1.15	0.82	0.81	-1.03	-1.58	-0.49	0.001	-0.34	-0.81 0.12	0.140

CBT: Cognitive behavioral therapy; SIGHA: Structured Interview Guide for the Hamilton Anxiety Rating Scale; CGI: Clinical Global Impressions Scale; PAS: Panic and Agoraphobia Scale; BSI: Brief Symptom Inventory; * Cohens d = post minus baseline difference divided by the standard deviation at baseline of the total sample (n = 369). Confidence intervals and p-values based on linear regression; ** Based on linear regression, adjusted for an outcome's baseline values.

3.3.2 Neurofunctional effects

Baseline effects prior to CBT. Full results are given in Table 5. For the entire experiment, we found a significant main effect of group that was driven by enhanced activation in the PD/AG+SAD group predominantly in the bilateral superior temporal pole (STP), left MTG, left inferior frontal operculum (IFO), left insula and right ACC. When including the factor CS in the analysis, PD/AG+SAD patients exhibited, among others, a stronger activation upon the CS+ within the left MTG as well as the right hippocampus compared to PD/AG-SAD patients particularly during the early acquisition.

Neuroplastic effects following CBT as a function of comorbidity. Full results are given in Table 6. In the longitudinal analysis, a significant group x time interaction was observed during the acquisition phase within the left STP, strongly overlapping with the activation cluster that was identified in the baseline analysis. Prior to treatment, PD/AG+SAD patients showed a higher activation than PD/AG-SAD patients, which was reduced after treatment, whereas there was a slight, yet significant increase in activation within the PD/AG-SAD group. After treatment, both groups did not differ significantly anymore. During the extinction phase, the bilateral IFO (overlapping with the left IFO cluster as identified in the baseline analysis) as well as the left amygdala showed a similar activation pattern for the group x time interaction effect. PD/AG+SAD patients showed a significant reduction in brain activation from baseline to post, even below the level of PD/AG-SAD patients.

Table 5. Brain activation clusters during fear conditioning and extinction in patients with panic disorder and agoraphobia with (PD/AG+SAD) or without comorbid social anxiety disorder (PD/AG-SAD) at baseline (prior to CBT).

Contrast/Region	Side	Voxels	x	y	z	F or t	p uncorr.
Main effect Group							
Overall							
Superior temporal pole	L	672	-50	8	-18	18.65	< 0.001
Superior temporal pole	R	281	52	10	-20	17.77	< 0.001
Middle temporal gyrus	R	216	68	-24	-8	11.40	0.001
Post-hoc t-contrast: PD/AG+SAD > PD/AG-SAD							
Superior temporal pole	L	969	-50	8	-18	4.32	< 0.001
Superior temporal pole	R	997	52	10	-20	4.22	< 0.001
Middle temporal gyrus	L	221	-52	-52	14	3.42	< 0.001
Inferior frontal operculum	L	196	-46	18	14	3.42	< 0.001
Insula	L	145	-24	-32	20	3.35	< 0.001
Anterior cingulate gyrus	R	191	16	26	16	3.31	< 0.001
Middle temporal gyrus	L	159	-54	-48	-6	2.95	0.002

Post-hoc t-contrast: PD/AG-SAD > PD/AG+SAD						No differential activation	
Acquisition							
Superior temporal pole	L	688	-52	4	-16	22.15	< 0.001
Postcentral gyrus	L	326	-26	-30	40	16.91	< 0.001
Inferior frontal operculum	R	655	30	20	30	14.09	< 0.001
Superior temporal pole	R	194	50	10	-20	13.78	< 0.001
Inferior frontal operculum	L	221	-34	10	28	12.93	< 0.001
Post-hoc t-contrast: PD/AG+SAD > PD/AG-SAD							
Superior temporal pole	L	1014	-52	4	-16	4.71	< 0.001
Cerebellum	L	497	-16	-54	20	4.29	< 0.001
Postcentral gyrus	L	764	-26	-30	40	4.11	< 0.001
Inferior frontal operculum	R	1205	30	20	30	3.75	< 0.001
Superior temporal pole	R	712	50	10	-20	3.71	< 0.001
Inferior frontal operculum	L	614	-34	10	28	3.60	< 0.001
Post-hoc t-contrast: PD/AG-SAD > PD/AG+SAD						No differential activation	
Extinction[1]							
Anterior cingulate gyrus	R	192	16	26	16	12.09	0.001
Post-hoc t-contrast: PD/AG+SAD > PD/AG-SAD							
Superior temporal pole	R	193	52	12	-22	3.73	< 0.001
Inferior frontal operculum	L	184	-48	18	12	3.65	< 0.001
Anterior cingulate cortex	R	299	16	26	16	3.48	< 0.001
Post-hoc t-contrast: PD/AG-SAD > PD/AG+SAD						No differential activation	
Interaction effect Group x CS							
Acquisition[2]							
Middle temporal gyrus	L	4454	-40	-54	16	21.55	< 0.001
Superior occipital gyrus	L	357	-18	-76	32	16.04	< 0.001
Precentral gyrus	L	274	-52	-2	42	15.83	< 0.001
Middle temporal gyrus	L	985	-50	0	-22	15.33	< 0.001
Caudate nucleus	R	809	24	-22	22	14.28	< 0.001
Middle temporal gyrus	R	975	56	-58	2	12.98	< 0.001
Calcarine	R	1759	12	-64	10	12.82	< 0.001
Middle cingulate gyrus	L	237	-14	-30	28	12.43	< 0.001
Superior parietal gyrus	L	207	-26	-52	68	12.02	0.001
Superior parietal gyrus	R	211	28	-52	66	11.40	0.001
Insula	L	198	-28	-24	16	10.30	0.001
Post-hoc t-contrast: PD/AG+SAD > PD/AG-SAD CS+>CS-							
Middle temporal gyrus	L	13823	-40	-54	16	4.64	< 0.001
Middle temporal gyrus	L	1747	-50	0	-22	3.91	< 0.001
Caudate nucleus	R	1488	24	-22	22	3.78	< 0.001
Angular gyrus	R	1830	64	-50	32	3.77	< 0.001
Cerebellum	R	209	34	-40	-26	3.59	< 0.001
Superior parietal gyrus	R	355	28	-52	66	3.38	< 0.001
Hippocampus	R	208	38	-14	-20	3.27	0.001

Middle temporal gyrus	L	224	-60	-30	0	3.21	0.001
Post-hoc t-contrast: PD/AG+SAD > PD/AG-SAD CS->CS+							No differential activation
Extinction							
Superior parietal gyrus	R	252	24	-54	58	11.44	0.001
Post-hoc t-contrast: PD/AG+SAD > PD/AG-SAD CS+>CS-							
Superior parietal gyrus	R	511	24	-54	58	3.38	< 0.001
Post-hoc t-contrast: PD/AG+SAD > PD/AG-SAD CS->CS+							No differential activation

CBT: Cognitive behavioral therapy; L: left; R: right; CS+: stimulus associated with the unconditioned stimulus; CS-: CS not associated with the unconditioned stimulus; voxel: number of voxels per cluster; x, y, z: MNI coordinates; $p < 0.005$ (uncorr.) with a minimum cluster size of 142 contiguous voxels, indicating to correct for multiple comparisons at $p < 0.05$; Overall: Clusters differentially activated regardless of phase. We don´t report overall effects for interactions including the CS due to the CS being specific for the experimental phase
[1] refers to early extinction phase
[2] refers to early acquisition phase

When including the CS as a third factor, we found a significant three-way interaction of group x time x CS during the early acquisition within the MTG that overlapped with the activation cluster identified in the baseline analysis. This was driven by a strong activation upon the CS+ within the PD/AG+SAD group at baseline. Only PD/AG+SAD patients differentiated between the CS+ and CS- at baseline on the level of MTG activation and showed significantly stronger activation towards the CS+ compared to PD/AG-SAD patients. After treatment, the activation upon the CS+ was reduced significantly in PD/AG+SAD patients to the level of PD/AG-SAD patients. No significant differences or changes in activation of the MTG were observed within the PD/AG-SAD group.

The three-way interaction group x time x CS was significant during the early acquisition phase for the right hippocampus, too. At baseline, PD/AG+SAD patients showed stronger activations towards the CS+ than the CS-, while an inverse pattern was observed in PD/AG-SAD patients. At post, no differences in activation patterns between groups and stimuli were observed anymore. Changes from baseline to post as a function of group and the interaction of group*CS are visualized in Figure 2.

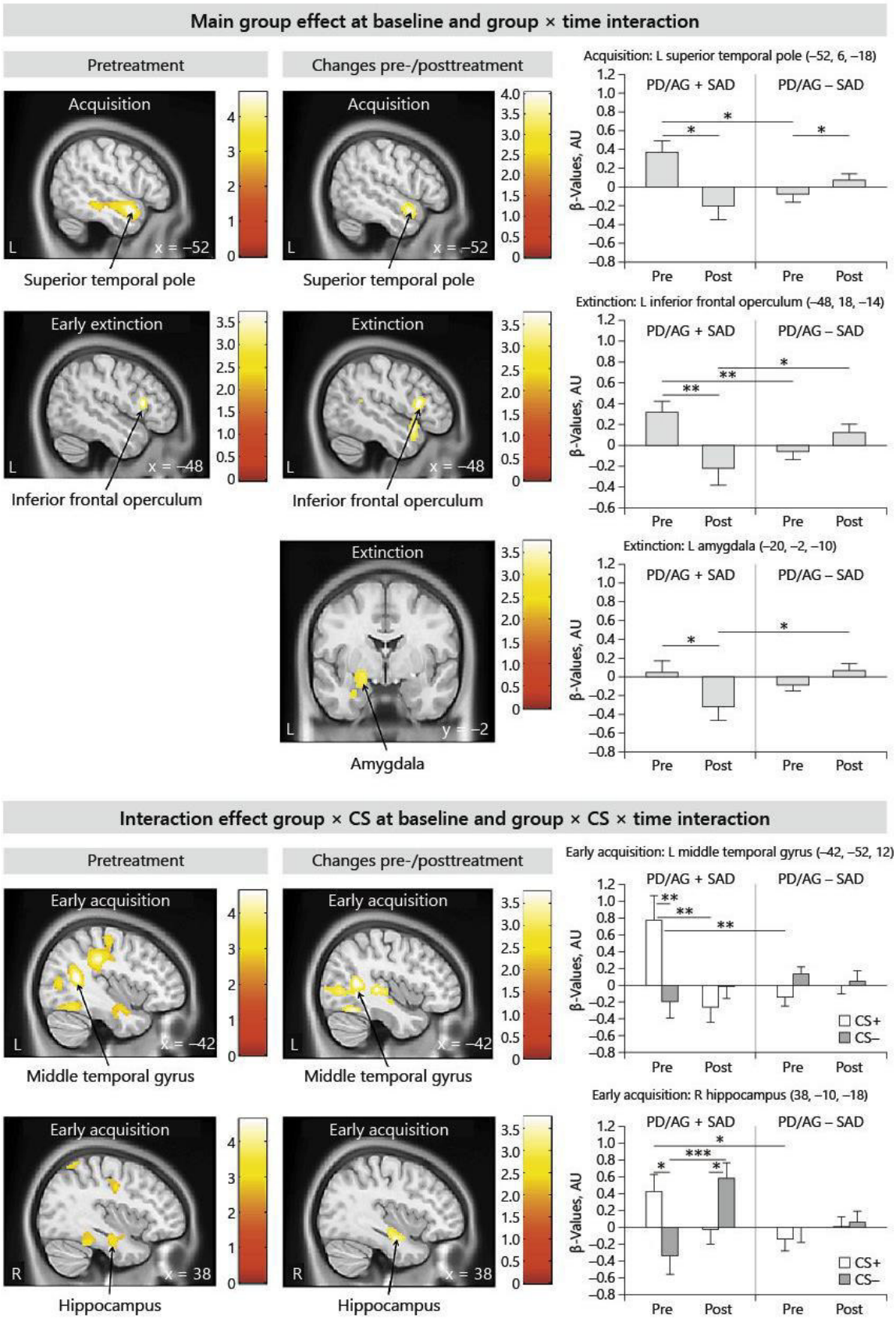


Figure 2. For figure legend, see next page

Figure 2. Brain activation clusters differentially activated during fear conditioning and extinction in patients with panic disorder and agoraphobia with (PD/AG+SAD) or without comorbid social anxiety disorder (PD/AG-SAD) prior to and after exposure-based cognitive-behavioral therapy. The corresponding bar graphs show β-values for the peak voxels extracted from a 5-mm sphere over the time course (pre/post) as well as group differences and differences regarding the conditioned stimuli. Error bars indicate the standard error of the mean. L, left; R, right; CS+, stimulus associated with the unconditioned stimulus; CS–, CS not associated with the unconditioned stimulus; AU, arbitrary units. MNI coordinates in parentheses; $p < 0.005$ (uncorr.) with a minimum cluster size of 142 contiguous voxels, indicating to correct for multiple comparisons at $p < 0.05$ (Monte Carlo simulation). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 6. Brain activation clusters during fear conditioning and extinction in patients with panic disorder and agoraphobia with (PD/AG+SAD) or without comorbid social anxiety disorder (PD/AG-SAD) prior to and after exposure-based cognitive behavioral therapy

Contrast/Region	Side	Voxels	x	y	z	F or t	p uncorr.
Interaction effect Group x Time							
Overall							
Superior temporal pole	L	385	-48	10	-18	15.87	< 0.001
Superior temporal gyrus	L	163	-54	-46	14	13.42	< 0.001
Superior temporal gyrus	R	400	52	-28	0	11.22	0.001
Inferior frontal operculum	R	365	52	20	14	11.19	0.001
Post-hoc t-contrast: PD/AG+SAD > PD/AG-SAD (T1 > T2)							
Superior temporal pole	L	972	-48	10	-18	3.98	< 0.001
Cerebellum	R	175	10	-44	-14	3.66	< 0.001
Superior temporal gyrus	L	368	-54	-46	14	3.66	< 0.001
Superior temporal pole	R	199	50	10	-18	3.54	< 0.001
Superior temporal gyrus	R	782	52	-28	0	3.35	< 0.001
Inferior frontal operculum	R	939	52	20	14	3.35	< 0.001
Inferior temporal gyrus	L	178	-50	-28	-18	3.32	< 0.001
Superior temporal gyrus	L	154	-48	-28	4	2.93	0.002
Post-hoc t-contrast: PD/AG-SAD > PD/AG+SAD (T1 > T2)						No differential activation	
Acquisition							
Superior temporal pole	L	168	-52	6	-18	16.18	< 0.001
Vermis		159	6	-42	-16	14.45	< 0.001
Post-hoc t-contrast: PD/AG+SAD > PD/AG-SAD (T1 > T2)							
Superior temporal pole	L	245	-52	6	-18	4.02	< 0.001
Vermis		250	6	-42	-16	3.80	< 0.001
Postcentral gyrus	L	254	-26	-28	42	3.40	< 0.001
Middle temporal gyrus	R	189	60	-38	-8	3.25	0.001
Superior frontal gyrus	R	393	18	10	48	3.13	0.001
Superior frontal gyrus, orbital	R	147	22	16	-16	3.09	0.001
Post-hoc t-contrast: PD/AG-SAD > PD/AG+SAD (T1 > T2)						No differential activation	
Extinction							
Inferior frontal operculum	R	210	54	18	12	14.12	< 0.001
Inferior frontal operculum	L	192	-46	18	14	13.93	< 0.001

Post-hoc t-contrast:							
PD/AG+SAD > PD/AG-SAD (T1 > T2)							
Inferior frontal operculum	R	478	54	18	12	3.76	< 0.001
Inferior frontal operculum	L	319	-46	18	14	3.73	< 0.001
Superior temporal gyrus	L	234	-54	-46	16	3.63	< 0.001
Superior temporal pole	L	248	-46	14	-16	3.40	< 0.001
Superior temporal gyrus	R	248	50	-28	0	3.35	< 0.001
Amygdala	L	151	-20	-2	-10	3.01	0.001
Post-hoc t-contrast:							
PD/AG-SAD > PD/AG+SAD (T1 > T2)						No differential activation	
Interaction effect Group x Time x CS							
Acquisition[1]							
Middle temporal gyrus	L	240	-42	-52	12	13.90	< 0.001
Cerebellum[2]	L	819	-12	-76	-18	13.63	< 0.001
Cerebellum	R	195	10	-70	-18	12.53	< 0.001
Lingual gyrus	R	181	22	-50	-2	12.44	< 0.001
Lingual gyrus	R	431	10	-64	8	12.20	0.001
Middle temporal gyrus	L	228	-44	-30	2	12.12	0.001
Precentral gyrus	L	342	-22	-18	60	11.70	0.001
Middle temporal gyrus	L	227	-52	-72	4	10.70	0.001
Post-hoc t-contrast:							
PD/AG+SAD > PD/AG-SAD: T1 > T2 (CS+ > CS-)							
Middle temporal gyrus	L	5012	-42	-52	12	3.73	< 0.001
Middle temporal gyrus	R	257	64	-12	-12	3.70	< 0.001
Middle temporal gyrus	R	267	44	-64	8	3.46	< 0.001
Precentral gyrus	L	830	-22	-18	60	3.42	< 0.001
Hippocampus	R	405	38	-10	-18	3.33	< 0.001
Paracentral lobule	R	149	14	-34	56	3.21	0.001
Middle temporal gyrus	R	168	64	-42	6	3.19	0.001
Middle frontal gyrus	R	143	26	36	42	3.18	0.001
Post-hoc t-contrast:							
PD/AG-SAD > PD/AG+SAD: T1 > T2 (CS+ > CS-)						No differential activation	
Full Extinction							
Precentral gyrus	R	591	30	-20	46	19.41	< 0.001
Middle cingulate gyrus	L	252	-18	-44	52	12.76	< 0.001
Superior parietal gyrus	R	142	32	-60	56	11.00	0.001
Post-hoc t-contrast:							
PD/AG+SAD > PD/AG-SAD: T1 > T2 (CS+ > CS-)							
Precentral gyrus	R	1620	30	-20	46	4.41	< 0.001
Superior parietal gyrus	R	259	32	-60	56	3.32	< 0.001
Post-hoc t-contrast:							
PD/AG-SAD > PD/AG+SAD: T1 > T2 (CS+ > CS-)						No differential activation	

L: left; R: right; CS+: stimulus associated with the unconditioned stimulus; CS-: CS not associated with the unconditioned stimulus; voxel: number of voxels per cluster; x, y, z: MNI coordinates; $p < 0.005$ (uncorr.) with a minimum cluster size of 142 contiguous voxels, indicating to correct for multiple comparisons at $p < 0.05$; Overall: Clusters differentially activated regardless of phase. We don´t report overall effects for interactions including the CS due to the CS being specific for the experimental phase.

[1] refers to early acquisition phase

[2] cluster encompassing the left fusiform face area

3.4 Discussion

Comorbidity of mental disorders is a phenomenon that clinicians frequently have to deal with when deciding for the treatment of choice (Dell'Osso & Pini, 2012; Wittchen et al., 2011). The major aims of the present study were to identify clinical and neural substrates of secondary SAD in primary PD/AG and whether exposure-based CBT specifically tailored to target PD/AG symptoms also alters secondary SAD symptomatology. Main findings were: a) Clinically, CBT tailored to target primary PD/AG works equally well in patients with or without comorbid SAD and appears to generalize also to SAD symptomatology; b) on a neural level, we identified a specific neural signature, associated with comorbidity of SAD in primary PD/AG that predominantly extended throughout the ventral object recognition pathway within the temporal lobe as well as the defensive system network encompassing e.g. the amygdala, hippocampus and the IFO; c) in line with the observed clinical effects, this signature was reduced by means of CBT.

Exposure-based CBT is an effective approach for the treatment of anxiety disorders like PD/AG and SAD (Craske et al., 2017; Hofmann et al., 2012; Hofmann & Smits, 2008). The present clinical results show that PD/AG-specific CBT leads to a reduction of primary PD/AG and secondary SAD symptomatology, as indicated by a parallel reduction of SIGH-A scores within both groups after treatment as well as the attenuation of BSI interpersonal sensitivity scores of PD/AG+SAD patients to the level of PD/AG-SAD patients. One may argue that the shared pathogenic mechanisms in both disorders favour the idea of an overarching mechanism involving fear-inhibitory learning as induced by behavioral exposure leading to effects within both disorders even though only PD/AG symptoms were specifically targeted. Moreover, general effects of psychotherapy like sense of control or therapeutic bond might have been involved in the effects observed here (Grawe, 2000; Orlinsky & Howard, 1987). However, cognitions feared by social anxious patients were not specifically targeted during exposure. It is possible that the reduction in SAD symptomatology may be due to transfer effects from PD/AG symptomatology to social fears. Unfortunately, information regarding this putative generalization effect in patients' every-day life was not gathered, such that this hypothesis yet remains speculative. Future studies should more strongly focus on the possibility that exposure may indeed generalize to other fears in patients suffering from more than one anxiety disorder. Although no direct proof of evidence can be given by the present data, the potential of exposure to induce generalization beyond the targeted fears would support the use of transdiagnostic treatment manuals for comorbid anxiety patients. This would open up the possibility that, once the basic principles of fear inhibitory learning have been internalized, a certain degree of generalization

may take place. Previously, a positive effect of exposure-based CBT on secondary depressive symptoms in this sample has been reported (Emmrich et al., 2012). While the treatment protocol appears to affect symptoms of both anxiety and depression that lie beyond the originally targeted PD/AG symptomatology, the putative mechanisms behind may differ between symptom alleviation of depression vs. social fears.

One possibility to study these underlying mechanisms is the investigation of neurofunctional changes as a function of CBT and comorbidity. As previously described for depressive comorbidity in PD/AG (Lueken et al., 2015), we were here able to detect a specific neural signature which is associated with secondary SAD in PD/AG. While patients with a comorbid depressive disorder showed signs of altered PFC functionality (Lueken et al., 2015), the SAD signature can be characterized by two functional systems: the first system encompasses activations in the temporal lobe comprising the STP, the MTG, and occipitotemporal brain regions. The latter two are related to the ventral object recognition pathway, that is proposed to extend throughout the inferior and middle parts of the temporal lobe starting from the primary visual cortex in the occipital lobe (Gilbert, 2013; Van Essen & Gallant, 1994). It is associated with the recognition of form and colour, but also more complex stimuli including faces. Similarly, the STP, which represents an output region of the ventral object recognition pathway (Albright, 2013), is known to be involved in object representation, processing and polysensory integration (Peelen & Caramazza, 2012; Tyler et al., 2004; Visser, Jefferies, & Ralph, 2010). Results from lesion studies consider Brodman Areas 20 (inferior temporal gyrus) and 21 (middle temporal gyrus) to be the most probable sites leading to a prosopagnosia when being damaged (Kolb & Whishaw, 1980). As attentional biases concerning faces have been proposed in SAD patients (Gilboa-Schechtman, Foa, & Amir, 1999; Mansell, Clark, Ehlers, & Chen, 1999), increased activation in these regions prior to therapy could also represent a pathogenic feature of comorbid SAD indicating exaggerated processing of visually salient cues.

The second component of the SAD-specific signature corresponds to the defensive system network represented here by the anterior insula / IFO, and hippocampus. Even though this network is known to be activated in PD/AG (Kircher et al., 2013), it appeared to be more strongly activated in patients suffering from secondary SAD. As this network also confers the neural processes underlying fear conditioning, enhanced activation in patients suffering from PD/AG and SAD could indicate stronger conditionability as a function of disease load. In our study, PD/AG+SAD patients showed a higher activation in response to the CS+ within the MTG

and the hippocampus during the acquisition phase prior to treatment, possibly indicating a stronger sensitivity to form associations between CS and US.

CBT-specific effects on changes in neurofunctional activation patterns predominantly affected these two systems: enhanced activation in the ventral object recognition pathway as a function of comorbidity was effectively reduced to the level of patients without comorbidity following CBT. The same pattern applied to the IFO and hippocampus, representing defensive network components. As to the amygdala, we did not observe enhanced activation prior to CBT in comorbid patients per se, but the amygdala was particularly sensitive to change with PD/AG+SAD patients showing a pronounced inhibition of the amygdala even below the level of activation in PD/AG-SAD patients after CBT. This stronger decrease in activation in PD/AG+SAD patients might partly be due to ceiling effects regarding the activity of the defensive system structures at baseline.

Our results can also be interpreted with respect to the emerging topic of Research Domain Criteria (RDoC) (Cuthbert & Insel, 2013; Insel et al., 2010). As the RDoC initiative tries to integrate biological and psychological approaches to establish a new taxonomy for mental disorders (Kozak & Cuthbert, 2016), its' domains may also serve to explain the results reported here. The overlap in brain activity within PD/AG and SAD might also be due to the overlap regarding the related RDoC domain of negative valence systems. More precisely, this refers to the subordinate construct of acute threat that is relevant for both disorders (Bas-Hoogendam et al., 2016; Hamm et al., 2016). The differences in brain activation we observed between PD/AG and SAD might be related to the domain of cognitive systems including the construct of perception as well as the social processes domain and its' subordinate construct of social communication, where object recognition including facial perception plays a pivotal role. Although to date there are no scientific publications directly investigating the relevance of those two RDoC constructs in SAD patients, previous studies and clinical practice indicate that SAD patients exhibit altered perception of faces (Gilboa-Schechtman et al., 1999) as well as difficulties in social communication (DSM-V, 2013). Those differences might therefore account for the altered brain activation in response to salient visual cues in occipital and temporal brain regions we observed here. Furthermore, shared RDoC domains might have provoked the similar effects of CBT in both disorders, supporting the assumption of an overarching treatment mechanism in exposure therapy that effectively targets the RDoC construct of acute fear and thus crosscutting different anxiety disorders.

Methods limitations

Our findings have to be interpreted in light of the study's limitations. As this was a post-hoc analysis, we did not have the opportunity to include a primary SAD group to study the effects of primary SAD without PD/AG. Furthermore, we had to refer to the BSI subscale interpersonal sensitivity as a proxy measure for social anxiety symptomatology. Even though there are significant correlations with well-known social anxiety questionnaires, we recommend the use of established measures for social anxiety in future studies which address similar research questions. Moreover, we studied the effects of current SAD comorbidity regardless of possible previous lifetime SAD and thus neglecting potential effects of such past disorders.

The sample size represents another limitation that might result in underpowered analyses. Especially the PD/AG+SAG group was rather small with just 14 patients included in the fMRI sample. On the other hand, clinical effects in the completer sample of 242 patients were mirrored in the reduced MRI sample. By enlarging sample size and thus statistical power, future investigators may be able to further specify the neural signatures of secondary SAD in primary PD/AG. Nevertheless, the fact that we were able to find significant differences in a small sample indicates the effect size to be pronounced.

As mentioned previously, Monte-Carlo simulations, like the one established here, have recently been criticized as they may facilitate false-positive results (Eklund et al., 2016). Due to reasons of comparability between all "Panic-Net" studies the correction method for multiple comparisons was maintained for the present investigation. However, with respect to Eklund et al. (2016), our results have to be treated as preliminary results and need further replication in a larger sample.

3.5 Conclusion

In this study, we were able to highlight the moderating effects of comorbidity on treatment outcome in PD/AG. On a clinical level, we observed that PD/AG-specific treatment bears potential to generalize to secondary SAD symptomatology, thus favouring the idea of a general mechanism that may foster the transfer of fear-inhibitory learning experiences. On a neural level, results demonstrate a specific neural signature to be associated with secondary SAD, encompassing two functional systems: First, this signature extends throughout the ventral object recognition pathway, which is known to be related to the recognition of social cues and thus

SAD symptomatology. Second, comorbid SAD further amplifies the activation of defensive system structures. Both functional systems were effectively targeted by CBT, resulting in attenuated activation patterns to the level of patients without SAD comorbidity. Our results can be seen as encouraging for further research as well as clinical practice as they indicate that exposure-based CBT is a powerful approach for treating PD/AG accompanied by comorbid SAD and leads to a symptom reduction extending to the neural level in both disorders even though only PD/AG is specifically targeted. Therefore, treatment outcome seems to be unaffected by comorbidity between those two anxiety disorders. Described within the picture of the Parable of the Sower, richness of soil is not impaired by comorbidity of anxiety disorders thus leading to similar treatment outcome in PD-patients with and without secondary SAD. Future studies are encouraged to investigate the commonalities and differences between comorbid conditions more in-depth and to identify common pathways of change that possibly follow overarching functional domains as laid out by the RDoC framework. Identifying these may help to better cover comorbidities, thus supporting personalized and time-efficient treatment options particularly for patients suffering from more than one anxiety disorder.

4 Resting-state signatures moderating treatment response in spider phobia

4.1 Theoretical background

Even though exposure-based CBT provides a powerful approach for treating anxiety disorders, a substantial proportion of patients does not respond in a clinically meaningful way (Loerinc et al., 2015; Taylor et al., 2012). As anxiety disorders, and specific phobia in particular, are very frequent (Wittchen et al., 2011), this results in a high number of patients left with unsatisfactory treatment outcome and thus further suffering and disability. On the other hand, there are also many patients that achieve substantial improvement of symptoms or even full remission via exposure-based CBT, which highlights its efficacy and the accuracy of its theoretical assumptions (Bandelow, Lichte, et al., 2014; Carpenter et al., 2018). The discrepancy in outcomes of the very same treatment points to differences within the population of patients with respect to their susceptibility towards the main mechanism of action of exposure treatment. Therefore, the identification of pre-treatment patient characteristics that moderate fear extinction and inhibitory learning is essential. It might enable patient stratification, the personalized application of modified or add-on treatments and thus the improvement of response rates.

Exposure-based CBT owes its efficacy to the tremendous scientific efforts that have been made with respect to the underlying neurobiology of anxiety disorders (Duval et al., 2015) and the way how fear extinction via exposure treatment alters those neural substrates (Messina et al., 2013; Vervliet et al., 2013). With respect to specific phobia, a network comprising the amygdala, MPFC, ACC, insula, and thalamus has been proposed to be hyperresponsive compared to healthy controls (Del Casale et al., 2012; Garcia, 2017; Ipser, Singh, & Stein, 2013; Münsterkötter et al., 2015; Peñate et al., 2017; Zilverstand, Sorger, Kaemingk, & Goebel, 2017). This is accompanied by decreased activation in medial and ventral prefrontal structures (Del Casale et al., 2012; Hermann et al., 2009; Hermann et al., 2007; Ipser et al., 2013; Schienle, Schafer, Hermann, Rohrmann, & Vaitl, 2007) thus confirming the hypothesized deficient emotion regulation of specific phobia patients (Del Casale et al., 2012). Especially regarding animal phobias, the results show high consistency (Del Casale et al., 2012; Peñate et al., 2017).

There is a substantial overlap of the neurocircuitry related to specific phobia and the structures that are commonly referred to as the defensive system network regarding the whole spectrum of anxiety disorders (Duval et al., 2015). The structures also highly correspond with

those involved in human fear extinction and thus the mechanism of action of exposure treatment (Vervliet et al., 2013). However, only little is known on the functional connections between the neural structures involved in specific phobia. Such connectivity measures may be advantageous in further clarifying the neural alterations related to pathological defensive responses that have been acquired e.g. via fear conditioning and how those signatures moderate treatment outcome. The few existing studies on (functional) connectivity in specific phobia point to functional decoupling of prefrontal and defensive system regions e.g. the amygdala (Åhs et al., 2009; Stefanescu, Endres, Hilbert, Wittchen, & Lueken, 2018) as it was demonstrated to characterize other anxiety disorders like SAD, PD/AG, and GAD as well (Geiger et al., 2016; Hahn et al., 2011; Kim et al., 2011; Liao et al., 2010; Makovac et al., 2016; Pannekoek et al., 2013; Sylvester et al., 2012; Xu et al., 2019). The decoupling has been interpreted in terms of deficient emotion regulation (Stefanescu et al., 2018). Furthermore, decreased fronto-striatal connectivity has been demonstrated in specific phobia compared to healthy controls suggesting an altered information flow in those patients (Scharmüller et al., 2013). However, all those studies in specific phobia used task-based approaches including the presentation of phobic stimuli. Therefore, connectivity within the resting brain of specific phobia patients remains largely unknown even though this would provide insights in persisting alterations in the absence of the phobic stimulus as it is for example the case when patients avoid confrontations with the feared stimulus. Furthermore, it is unclear how rsFC moderates treatment outcome in specific phobia patients. Analysing rsFC may constitute an innovative approach for studying the neural correlates of specific phobia and the way how those correlates moderate treatment outcome. Therefore, the present investigation aimed at identifying pre-treatment resting-state connectivity signatures that differ between responders and non-responders with respect to exposure treatment in spider phobia.

Based on the existing knowledge on neural alterations in specific phobia, the dual-process- and inhibitory learning model as well as the studies on potential (resting-state) predictors of treatment outcome in other anxiety disorders, we set up the following hypotheses for the present investigation:

a) Responders – whether classified according to a self-assessment questionnaire or a behavioral avoidance test (BAT) – as well patients exhibiting high within-session extinction (WS-ext) should be characterized by enhanced inhibitory connectivity between frontal and defensive-system structures compared to non-responders / low WS-ext patients.

b) We expected the amygdala to exhibit significantly stronger inhibitory connectivity with frontal regions in responders / high WS-ext patients compared to non-responders / low WS-ext patients.
c) Furthermore, connectivity between ACC and amygdala should be stronger in responders / high WS-ext patients compared to non-responders / low WS-ext patients.
d) Responders / high WS-ext patients should exhibit enhanced involvement of frontal structures within the bilateral FPN/ECN compared to non-responders / low WS-ext patients.
e) Regarding the DMN, we expected to observe less anterior-posterior dissociation in responders / high WS-ext patients compared to non-responders / low WS-ext patients, which should be reflected in decreased connectivity within the anterior as well as increased connectivity within the posterior portions of the DMN.
f) Heightened participation of the ACC within the SN was expected to characterize responders / high WS-ext patients compared to non-responders / low WS-ext patients.

4.2 Methods

4.2.1 Participants and recruitment pathway

Patients were recruited via press releases of the University Hospital of Würzburg and the related media coverage in local newspapers, radio or on internet platforms. Furthermore, flyers and posters were distributed across specialized local outpatient centres, medical practices and public buildings. Recruitment pathways were supplemented by digital advertisements upon social media platforms and university recruitment systems. For details regarding recruitment and drop-out rates please see the CONSORT flowchart depicted in Figure 3. The study has been conducted in accordance with the Declaration of Helsinki and has been approved by the ethics committees of the medical faculties at University of Würzburg (proposal number 330/15) and University of Münster (proposal number 216-212-b-S). All participants provided written informed consent and were compensated with 100€ after completion of the six study visits. The study has been registered at ClinicalTrials.gov (registration ID: NCT03208400).

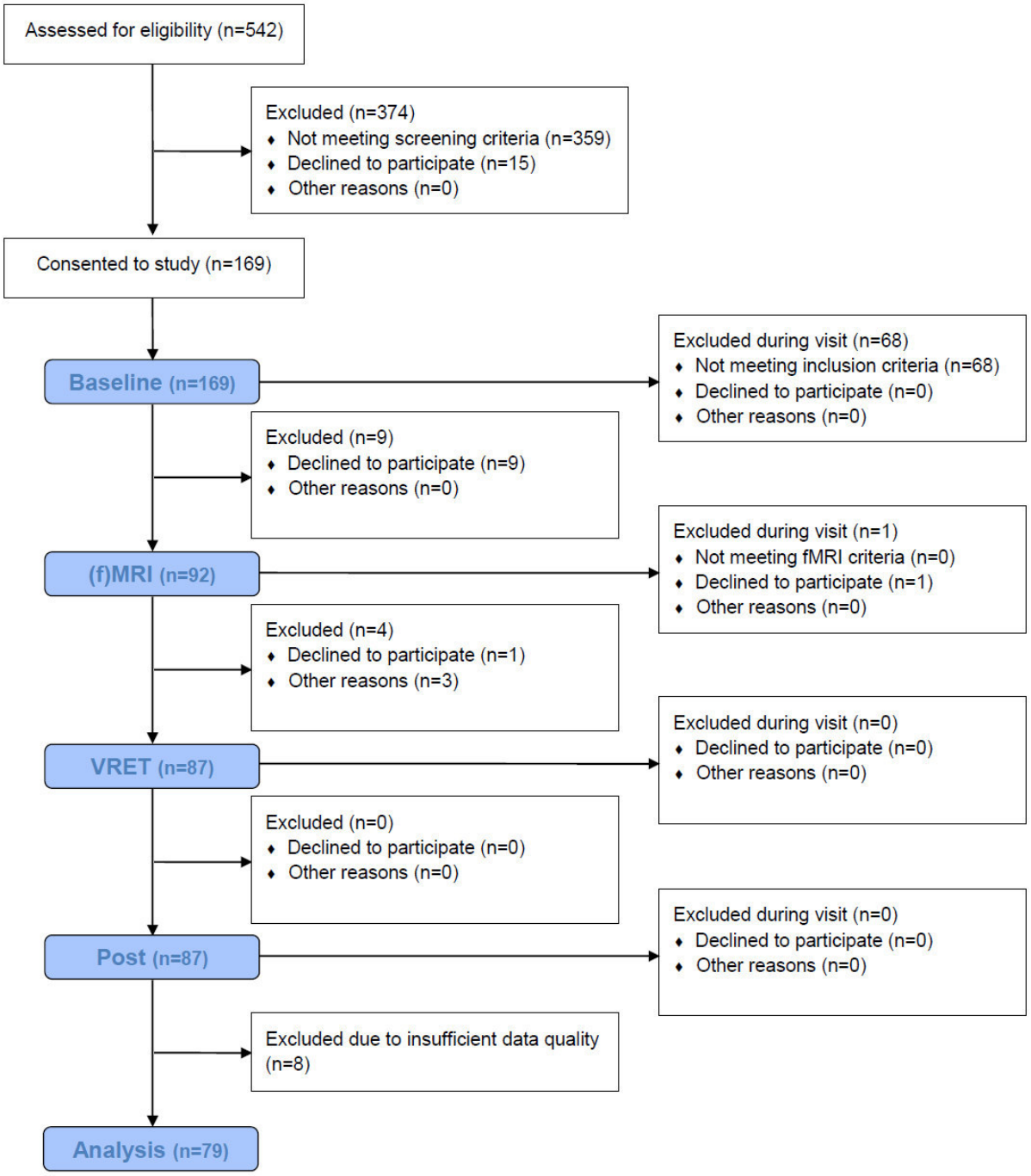


Figure 3. CONSORT-Flowchart

Patients were diagnosed with spider phobia. Fulfilment of DSM-IV-TR diagnostic criteria for specific phobia, animal subtype (DSM Code: 300.29) was assessed via the German version of the structured clinical interview for DSM-IV-TR (SCID Axis I; Wittchen et al., 1997). Only right-handed adults aged 18 to 65 years that were fluent in German language and willing to participate in a VRET were included. Furthermore, patients had to be of Caucasian descent back to maternal and paternal grandparents due to the related (epi-)genetic analyses. Lifetime diagnosis of comorbid mental disorders including PD, AG, SAD, GAD, obsessive

compulsive disorder, PTSD, severe major depression, bipolar disorder (I/II), borderline personality disorder, any psychotic or substance-use disorder (except for nicotine), acute suicidality, current (psycho-)pharmacological treatment, current or past psychotherapy, any neurological diseases, current pregnancy, or fulfilment of MRI-contraindications led to exclusion. Patients suffering from comorbid mild to moderate depression (unless currently treated psychotherapeutically or pharmacologically) and further specific phobias of the animal subtype were included as long as spider phobia was determined to be the primary diagnosis. Additionally, all patients needed to reach a Spider Phobia Questionnaire (SPQ; Klorman, Weerts, Hastings, Melamed, & Lang, 1974) Score > 19 to be included. This cut-off has been proposed to indicate clinical significance of symptom severity (Hamm, 2006; Öst, 1996).

4.2.2 Study protocol

The analysis presented here is part of the clinical study "SpiderVR", which was conducted within the scope of the Collaborative Research Center 58 "Fear, Anxiety, Anxiety Disorders" (www.dfg.de/gefoerderte_projekte/programme_und_projekte/listen/projektdetails/ index.jsp?id=44541416). SpiderVR aims at predicting treatment outcome among spider phobic patients via neurobiologically based machine learning. The following paragraphs will focus on the information relevant to the present investigation. For details regarding the whole study protocol please refer to Schwarzmeier et al. (2019).

The study comprised a total of six visits for each patient (see Figure 4). Prior to treatment, a baseline assessment was conducted including a structured clinical interview, a BAT, blood sampling as well as psychometric questionnaires and a CGI rating (Guy, 1976). The baseline assessment (Visit 1) was followed by two MRI sessions (Visits 2 + 3) from which only the first is relevant to the present analyses as it included the resting-state measurment. During the fourth visit, a one-session massed exposure treatment was conducted in VR. Within seven days after VRET the post assessment (Visit 5) was conducted including again the BAT, blood sampling as well as psychometry and CGI rating. Six months after the post assessment the follow-up (Visit 6) took place comprising the same elements as baseline and post-assessment. An overview of all assessments (grouped for timepoint and type of measurement) can be found in Appendix B.

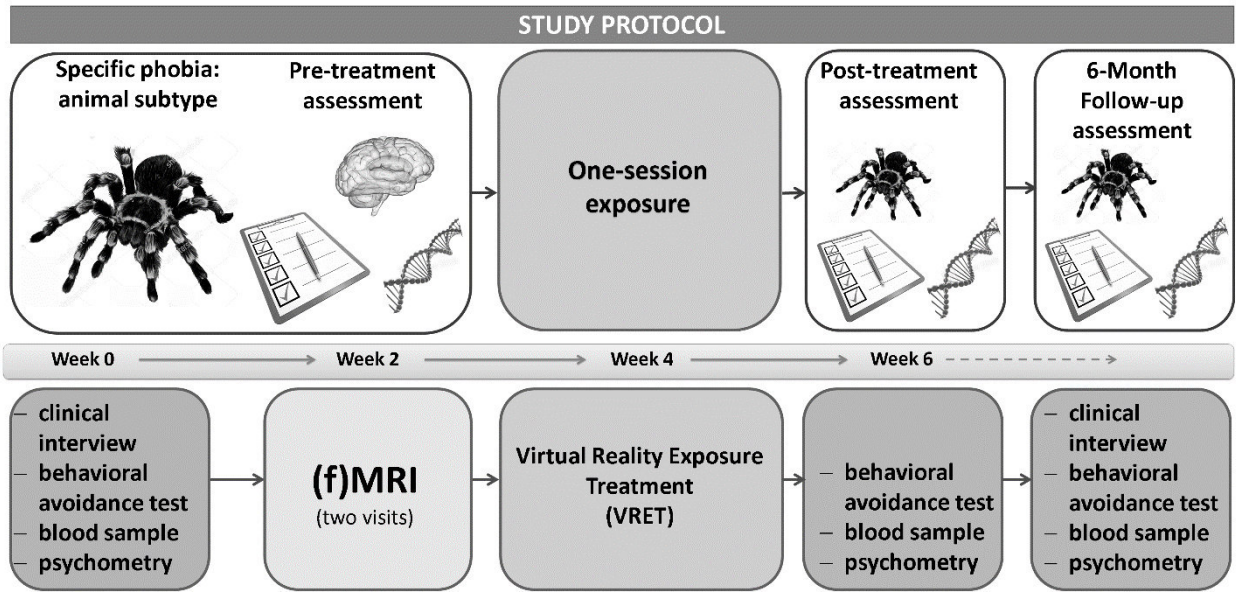


Figure 4. Study protocol of the SpiderVR study (modified from Schwarzmeier et al., 2019).

Telephone screening

Prior to the baseline assessment, every person that was interested in participating in the study unterwent a telephone screening for in- and exclusion criteria. We used a strucutred interview (Screening questions of the Composite International Diagnostic Interview; CAPI-WHO-CIDI; DIAX-CIDI version; Wittchen & Pfister, 1997) to screen for comorbid mental disorders. Patients who fulfilled all criteria were invited to attend the baseline assessment.

Baseline assessment

The first visit started with a detailed patient education on the study's aims, data protection, and potential risks. Afterwards, participants provided written informed consent. To ensure sufficient symptom severity, fulfilment of the SPQ cut-off score was tested subsequently. The results were calculated immediately. Participants that did not reach the cut-off score were excluded from further participation. In case the cut-off was reached, the SCID interview was conducted by trained personnel. If a primary specific phobia of the animal subtype spider was diagnosed, the patient remained within the sample. Otherwise and in case of any comorbidities, except for mild to moderate depression or secondary animal phobia, participants were excluded. Subsequently, the BAT was conducted, blood was drawn and the patients were asked to complete the psychometric battery via LimeSurvey (www.limesurvey.org). The baseline assessment was followed by the two MRI visits.

The detailed BAT protocol will be described along with the response classification methods under "4.2.3 Response classification and measures of the extinction process". Further information regarding the related (epi-)genetic analyses and task-based fMRI measurements conducted during the visits 1-3 can be obtained from Schwarzmeier et al. (2019).

Virtual reality exposure treatment

Along with the second MRI visit, a detailed psychoeducational manual, which was adapted from Herrmann et al. (2017) was handed out to the patients. The manual, which served to prepare patients for VRET, comprised information on the (evolutionary) function of fear, its cognitive, behavioral, emotional and bodily components and their interplay, the vicious circle of fear, spider phobia as a form of anxiety disorder and the exposure rationale. Patients were asked to repeat the information they read in the beginning of visit 4 right before VRET started. Together with the therapist, the rationale of behavioral exposure was deduced and patients were informed about the induction of inhibitory learning (Craske et al., 2012) as central goal of the subsequent exposure treatment. If there were no further questions, patients completed a protocol assessing their expectations and apprehensions towards the upcoming exposure. Prior to entering the VRET scenarios, patients were informed about the technical aspects of the VR setup and were able to explore a spider-free room in order to ensure adequate moving skills within the virtual environment.

Afterwards, the actual VRET was started by the therapist. The whole procedure was manualized. All therapists received a special training prior to conducting their first treatment to ensure adherence to the treatment protocol. Over the whole recruitment phase, upcoming questions and difficulties that appeared during the conduction of VRET were discussed within telephone conferences under supervision of experienced clinicians. The virtual environment was rendered via the VT+ research systems software (VTplus GmbH, Würzburg, Germany) and generated by the Steam Source engine (Valve Corp., Bellevue, Washington, USA). The VR scenarios were displayed via a Z800 3D Visor head-mounted display (HMD; eMagin, NY, USA) over a maximum duration of 2.5 hours. The software provided a total of sixteen different scenarios. Each patient underwent the same five scenarios unless he/she declined further participation during exposure. The scenarios differed regarding size, number, positioning and movement of the spider(s) to support generalization. For a detailed description of the five VR scenarios please refer to Schwarzmeier et al. (2019). Prior to entering a scenario (anticipatory anxiety) and during the different scenarios patients were repeatedly asked to rate their fear

within a range of "0 = no fear at all" and "100 = extremely strong fear". Within each scenario the patient had to pass several behavioral anchor points (e.g. walking below a spider hanging from the doorframe) to further support standardization. If the fear rating provided by the patient during a scenario fell below 20 or the rating stagnated at least three times in succession, the next scenario was started by the therapist or VRET was terminated, respectively.

Post- and Follow-up assessment

Post assessment was conducted within seven days after VRET and comprised again the assessment of the two outcome measures (SPQ and BAT), blood sampling as well as psychometric questionnaires and a CGI rating. As mentioned above, the follow-up assessment took place at least six months after post assessment and comprised the same elements as the baseline assessment. Additionally, a follow-up questionnaire (for details see Schwarzmeier et al., 2019) was conducted to gather information on the percieved efficacy of the treatment and frequency of self-conducted exposure in the meantime. This thesis does not include any follow-up data and analyses.

4.2.3 Response classification and measures of the extinction process

A German translation of the Spider Phobia Questionnaire (Klorman et al., 1974) was determined to be the primary outcome measure as it is recommended for diagnostics of spider phobia within the treatment manual of Hamm (2006) and has been shown to exhibit satisfactory quality criteria especially with respect to test-retest-reliability (Muris & Merckelbach, 1996). The questionnaire comprises 31 assertions that can be ticked as "true" or "false". Each item is scored with either 0 or 1 resulting in a maximum score of 31. As recommended by Öst (1996), a score >19 was chosen as inclusion criterion to indicate clinically significant symptom severity. To be classified as a treatment responder, a patient had to exhibit a SPQ score reduction of at least 30% from baseline to post assessment or follow-up, respectively. The amount of reduction was determined by observing the resulting SPQ scores of the pilot patients. The SPQ represented the subjective response to exposure treatment.

An in vivo BAT served to determine the secondary outcome measure and thus the behavioral component of response. Previously, a living bird spider (*Grammostola rosea*) was placed in a closed plastic box. The box was then put on a wooden slide (Figure 5) with an initial distance of three meters between patient and spider. Subsequently, the patient was asked to drag the box towards himself as close as possible by using a crank. The remaining distance between patient and the box served to quantify avoidance behavior (in cm) and thus constituted the secondary outcome measure. Additionally, electrodermal activity was recorded during the BAT, fear ratings were obtained and standardized behavioral observations were noted. Those data were not included in the present analysis (for details refer to Schwarzmeier et al., 2019). To be classified as a treatment responder based on the BAT distance, a patient had to exhibit a distance reduction of at least 50% from baseline to post assessment or follow-up, respectively.

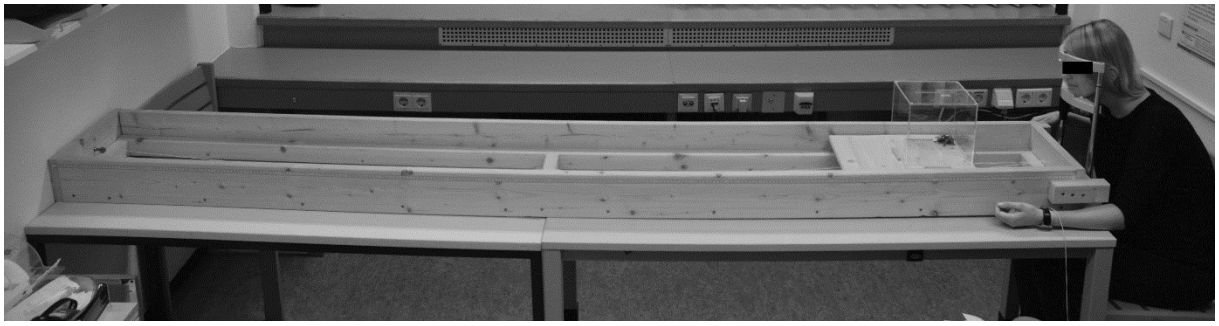


Figure 5. Setup Behavior Avoidance Test

Third, the amount of anxiety reduction, averaged across the different treatment scenarios, served as a measure of WS-ext and thus should represent a direct measure of inhibitory learning during treatment. Anxiety ratings were assessed over the whole VRET session. Within session extinction values were computed from the difference between maximum and minimum anxiety ratings as stated out by the patients within the respective scenario. WS-ext groups were formed via median split.

4.2.4 fMRI data acquisition and analysis

MR images were acquired using 3-T Siemens Skyra. A T1 structural image was collected from each participant via magnetization prepared rapid gradient echo (MPRAGE; matrix = 256 x 256, slices = 176, FOV = 256, voxel size = 1 x 1 x 1 mm, TE = 2.26 ms, TR = 1.9 s, flip angle = 9°). Resting state functional images were acquired in ascending order over a total duration of eight minutes (eyes closed) using a T2* weighted echo planar imaging sequence (EPI), which is sensitive to the blood oxygen level dependent contrast (BOLD; matrix = 64 x

64, slices = 33, FOV = 210, voxel size = 3.3 x 3.3 x 3.8 mm, slice thickness = 3.8mm, slice gap = 10%, TE = 30 ms, TR = 2.0 s, flip angle = 90°). All slices covered the whole brain and were positioned transaxially parallel to the anterior-posterior commissural line with a tilted angle of 20°. Stimuli were presented via MR-compatible LCD goggles and Presentation 14 (Neurobehavioral Systems; www.neurobs.de). Additionally, headphones were used for communication with the patients between the respective tasks.

All structural and functional images were preprocessed in CONN 18a (www.nitrc.org/projects/conn, RRID:SCR_009550) implemented in MATLAB, R2012b (MathWorks, Natick, Mass.) and SPM12 (www.fil.ion.ucl.ac.uk). The first five functional volumes were discarded to account for potential inhomogeneities in initial magnetization. Preprocessing (CONN defaultMNI pipeline) included functional realignment and unwarping, slice-timing correction, structural segmentation (grey matter, white matter, cerebrospinal fluid; CSF) and normalization to MNI space, functional normalization to MNI space, and smoothing (5mm FWHM Gaussian filter). As head motion can easily introduce spurious correlations into resting-state networks, we used the Artifact Detection Tools (ART, www.nitrc.org/projects/artifact_detect) implemented in CONN to identify outlier images. An image was considered an invalid scan (conservative settings, 95th percentile) if framewise head displacement exceeded 0.5 mm in any direction (x,y,z), or if global mean intensity for the respective image was more than three standard deviations from mean global signal intensity for the entire resting-state scan. Patients with more than 10% of invalid scans (here: > 23) were excluded from further analyses (n = 6). Invalid scans of the remaining patients were entered as individual 1st-level covariate (scrubbing).

After preprocessing, normalization of structural and functional images to MNI space was visually checked for each patient via CONN's "QA_NORM" function. Structural segmentation was also visually inspected for each patient via an overlay with the respective mask outline. Average time series for all regions of interest (ROI; Automated anatomical labelling atlas, AAL, www.gin.cnrs.fr/en/tools/aal/) were extracted from the unsmoothed dataset. The six rigid-body realignment parameters together with their first-order temporal derivatives, the effect of rest, patient-specific artefactual covariates (ART-based scrubbing) and white matter and CSF BOLD time series of each patient were removed from the BOLD signal via linear regression in order to reduce noise introduced by movements, physiological effects or the resting condition. A bandpass-filter was applied to the resulting BOLD time series (bounding box: 0.01Hz - 0.1Hz). The functional correlations were then checked for being normally distributed.

On the 1st-level, we performed ROI-to-ROI and Seed-to-Voxel analyses of functional connectivity (weighted GLM) by computing bivariate correlation maps with haemodynamic response function weighting. For group independent component analyses (ICA), we determined 20 components to be estimated. The degree of subject-level dimensionality reduction (number of subject-specific singular value decomposition components) was set to 64. Based on group and site comparisons (Würzburg - Münster) of sociodemographic characteristics ($\chi 2$- and t-tests, see Tables 7, 8 and 9), we introduced the baseline SPQ score, Age and the duration of exposure treatment as 2nd-level covariates of no interest. Responders and non-responders as well as high and low WS-ext patients were subsequently compared via unpaired t-tests. For seed-based 2nd-level analyses, we analysed the main effect of the respective bilateral seed regions. The different spatial ICA components were labelled via the computation of their spatial match to template as well as visual inspection. Six components were identified as noise components due to their extent over ventricles or restriction to the brain's edges. In total, we were able to identify the SN, bilateral FPN, DMN, extra-striate visual network, primary visual network as well as dorsal attention and sensory motor network. The cluster-threshold was set to $p < 0.05$ (FDR). The height-threshold for all analyses was set to $p < 0.001$ (uncorr.).

According to the hypothesis of deficient frontal regulation of defensive system structures in non-responders, predefined bilateral ROIs can be grouped into "defensive system related ROIs" and "executive control related ROIs". For the defensive system, we chose the amygdala, insula, ACC, hippocampus and thalamus as ROIs. With respect to executive control, we included the superior (SFG) and middle frontal gyrus (MFG; including their orbital and medial parts), the IFG pars opercularis, triangularis and orbitalis and the gyrus rectus as ROIs.

4.3 Results

4.3.1 Sample characteristics

Sample characteristics as well as descriptive data of the respective groups (SPQ, BAT, WS-ext) can be obtained from Tables 7, 8 and 9. SPQ and BAT groups overlapped (i.e. portion of responders according to both criteria) for 61.22%, SPQ and WS-ext for 59.18% as well as BAT and WS-ext for 53.48%.

Table 7. Demographic and clinical characteristics: resting state sample and SPQ responders/non-responders. Means (SD), except where noted.

	All patients (n = 79) 100%		SPQ Resp (n = 49) 62.03%		SPQ Non-Resp (n = 30) 37.97%		Chi^2 or t (df)	p
Demographic characteristics								
Female gender [n (%)]	68	(86.08)	41	(83.67)	27	(90.00)	0.621 (1)	0.431
Age (years)	29.16	(9.55)	27.16	(7.47)	32.43	(11.63)	2.218 (43.80)	< 0.05
Years of education	14.35	(3.32)	14.22	(3.67)	14.57	(3.28)	0.443 (77)	0.659
Clinical characteristics								
SPQ	23.08	(2.37)	23.61	(2.38)	22.20	(2.12)	-2.665 (77)	< 0.01
BAT final distance	172.51	(61.55)	181.99	(60.50)	157.02	(61.09)	-1.774 (77)	0.080
WS-ext	45.52	(18.94)	49.33	(18.13)	39.30	(18.86)	-2.353 (77)	< 0.05
Age of onset – SP (years) [1]	8.43	(4.06)	9.21	(4.30)	7.14	(3.30)	-2.372 (70.62)	< 0.05
Comorbidity	2	(2.53)	0	(0.00)	2	(6.67)	3.352 (2)	0.141
Major depression [n (%)]	1	(1.27)	0	(0.00)	1	(3.33)		
Secondary animal phobia [n (%)]	1	(1.27)	0	(0.00)	1	(3.33)		
CGI [n (%)]							11.219 (3)	< 0.05
Mildly ill	13	(16.5)	3	(6.12)	10	(33.33)		
Moderately ill	31	(39.2)	20	(40.82)	11	(36.67)		
Markedly ill	33	(41.8)	25	(51.02)	8	(26.67)		
Severely ill	2	(2.53)	1	(2.04)	1	(3.33)		
FEAS anxiety [2]	101.44	(14.31)	103.06	(14.91)	98.69	(13.03)	-1.310 (76)	0.194
FEAS disgust [2]	109.83	(12.09)	110.53	(13.12)	108.66	(10.22)	-0.660 (76)	0.511
STAI-Trait	36.85	(9.08)	37.24	(9.07)	36.20	(9.20)	-0.494 (77)	0.623
BDI-II total	3.68	(4.39)	3.67	(4.38)	3.70	(4.47)	0.026 (77)	0.979
ASI-3	15.90	(10.01)	15.39	(8.84)	16.73	(11.79)	0.539 (48.88)	0.592
Duration of VRET (min)	87.25	(25.21)	84.98	(24.41)	90.97	(26.46)	1.025 (77)	0.309
GSE	2.92	(0.41)	2.96	(0.36)	2.85	(0.49)	-1.177 (77)	0.243

SPQ: Spider Phobia Questionnaire; SD: Standard Deviation; Resp: Responders; Non-Resp: Non-Responders; BAT: Behavioral Avoidance Test; WS-ext: Mean within-session extinction values averaged across scenarios; SP: Specific Phobia; CGI: Clinical Global Impression Score; FEAS: Fragebogen zu Ekel und Angst vor Spinnen / Questionnaire on disgust and fear of spiders; STAI: State-Trait Anxiety Inventory; BDI-II: Beck Depression Inventory II; ASI-3: Anxiety Sensitivity Index 3; VRET: Virtual Reality Exposure Treatment; GSE: General Self-Efficacy Scale; n.s.: not significant at $p < 0.05$; [1] available for n = 77; [2] available for n = 78.

Table 8. Demographic and clinical characteristics of BAT responders/non-responders. Means (SD), except where noted.

	All patients (n = 79) 100%		BAT Resp (n = 39) 49.37%		BAT Non-Resp (n = 40) 50.63%		Chi^2 or t (df)	p
Demographic characteristics								
Female gender [n (%)]	68	(86.08)	31	(79.49)	37	(92.50)	2.790 (1)	0.095
Age (years)	29.16	(9.55)	29.0	(9.41)	29.32	(9.80)	0.150 (77)	0.881
Years of education	14.35	(3.32)	13.82	(3.52)	14.88	(3.97)	1.420 (75.04)	0.160
Clinical characteristics								
SPQ	23.08	(2.37)	23.28	(2.50)	22.87	(2.26)	-0.760 (77)	0.450
BAT final distance	172.51	(61.55)	165.78	(70.63)	179.06	(51.26)	0.958 (69.26)	0.341
WS-ext	45.52	(18.94)	47.79	(19.16)	43.31	(18.69)	-1.051 (77)	0.297
Age of onset – SP (years) [1]	8.43	(4.06)	9.7	(4.67)	7.25	(3.01)	-2.717 (60.75)	< 0.01
Comorbidity	2	(2.53)	0	(0.00)	2	(5.00)	2.001 (2)	0.157
Major depression [n (%)]	1	(1.27)	0	(0.00)	1	(2.50)		
Secondary animal phobia [n (%)]	1	(1.27)	0	(0.00)	1	(2.50)		
CGI [n (%)]							1.144 (3)	0.767
Mildly ill	13	(16.5)	7	(17.95)	6	(15.00)		
Moderately ill	31	(39.2)	13	(33.33)	18	(45.00)		
Markedly ill	33	(41.8)	18	(46.15)	15	(37.50)		
Severely ill	2	(2.53)	1	(2.56)	1	(2.50)		
FEAS anxiety [2]	101.44	(14.31)	102.39	(12.78)	100.53	(15.74)	-0.574 (76)	0.568
FEAS disgust [2]	109.83	(12.09)	108.76	(12.73)	110.85	(11.51)	0.760 (76)	0.450
STAI-Trait	36.85	(9.08)	37.38	(9.96)	36.33	(8.22)	-0.516 (77)	0.607
BDI-II total	3.68	(4.39)	3.69	(4.11)	3.68	(4.69)	-0.017 (77)	0.986
ASI-3	15.90	(10.01)	16.0	(9.94)	15.80	(10.21)	-0.088 (77)	0.930
Duration of VRET (min)	87.25	(25.21)	82.26	(23.71)	92.12	(25.96)	1.763 (77)	0.082
GSE	2.92	(0.41)	2.95	(0.41)	2.89	(0.42)	-0.683 (77)	0.497

BAT: Behavioral Avoidance Test; SPQ: Spider Phobia Questionnaire; SD: Standard Deviation; WS-ext: within-session extinction values averaged across scenarios; Resp: Responders; Non-Resp: Non-Responders; SP: Specific Phobia; CGI: Clinical Global Impression Score; FEAS: Fragebogen zu Ekel und Angst vor Spinnen / Questionnaire on disgust and fear of spiders; STAI: State-Trait Anxiety Inventory; BDI-II: Beck Depression Inventory II; ASI-3: Anxiety Sensitivity Index 3; VRET: Virtual Reality Exposure Treatment; GSE: General Self-Efficacy Scale; n.s.: not significant at $p < 0.05$; [1] available for n = 77; [2] available for n = 78.

Table 9. Demographic and clinical characteristics of high / low within-session extinction groups. Means (SD), except where noted.

	All patients (n = 79) 100%		high WS-ext (n = 40) 50.63%		low WS-ext (n = 39) 49.37%		Chi^2 or t (df)	p
Demographic characteristics								
Female gender [n (%)]	68	(86.08)	35	(87.50)	33	(84.62)	0.137 (1)	0.711
Age (years)	29.16	(9.55)	28.25	(8.72)	30.10	(10.37)	0.860 (77)	0.392
Years of education	14.35	(3.32)	14.68	(3.04)	14.03	(3.59)	-0.867 (74.35)	0.389
Clinical characteristics								
SPQ	23.08	(2.37)	23.07	(2.65)	23.08	(2.08)	0.004 (77)	0.997
WS-ext	45.52	(18.94)	60.55	(10.99)	30.12	(11.45)	-12.055 (77)	< 0.001
BAT final distance	172.51	(61.55)	169.69	(66.46)	175.40	(56.81)	0.410 (77)	0.683
Age of onset – SP (years) [1]	8.43	(4.06)	9.72	(4.09)	7.11	(3.62)	-2.964 (75)	< 0.01
Comorbidity	2	(2.53)	1	(2.50)	1	(2.56)	2.001 (2)	0.368
Major depression [n (%)]	1	(1.27)	1	(2.50)	0	(0.00)		
Secondary animal phobia [n (%)]	1	(1.27)	0	(0.00)	1	(2.56)		
CGI [n (%)]							2.127 (3)	0.546
Mildly ill	13	(16.5)	7	(17.50)	6	(15.38)		
Moderately ill	31	(39.2)	15	(37.50)	16	(41.03)		
Markedly ill	33	(41.8)	16	(40.00)	17	(43.59)		
Severely ill	2	(2.53)	2	(5.00)	0	(0.00)		
FEAS anxiety [2]	101.44	(14.31)	102.95	(12.22)	99.92	(16.15)	-0.933 (76)	0.354
FEAS disgust [2]	109.83	(12.09)	110.21	(13.56)	109.46	(10.58)	-0.270 (76)	0.788
STAI-Trait	36.85	(9.08)	36.88	(9.71)	36.82	(8.51)	-0.027 (77)	0.979
BDI-II total	3.68	(4.39)	3.55	(4.42)	3.82	(4.41)	0.272 (77)	0.786
ASI-3	15.90	(10.01)	16.80	(9.52)	14.97	(10.53)	-0.809 (77)	0.421
Duration of VRET (min)	87.25	(25.21)	85.40	(26.77)	89.15	(23.69)	0.659 (77)	0.512
GSE	2.92	(0.41)	2.93	(0.41)	2.90	(0.42)	-0.293 (77)	0.770

WS-ext: Within-session extinction values averaged across scenarios; BAT: Behavioral Avoidance Test; SPQ: Spider Phobia Questionnaire; SD: Standard Deviation; Resp: Responders; Non-Resp: Non-Responders; SP: Specific Phobia; CGI: Clinical Global Impression Score; FEAS: Fragebogen zu Ekel und Angst vor Spinnen / Questionnaire on disgust and fear of spiders; STAI: State-Trait Anxiety Inventory; BDI-II: Beck Depression Inventory II; ASI-3: Anxiety Sensitivity Index 3; VRET: Virtual Reality Exposure Treatment; GSE: General Self-Efficacy Scale; n.s.: not significant at $p < 0.05$; [1] available for n = 77; [2] available for n = 78.

4.3.2 Response criterion - SPQ

ROI-to-ROI

ROI-to-ROI analyses revealed two brain regions differentially connected to the left hippocampus when comparing SPQ-responders to SPQ-Nonresponders (see Figure 6 and Table 10 for an overview of all results concerning the response criterion SPQ). Responders exhibited significantly stronger inhibitory functional connectivity between the left hippocampus and orbital part of the left MFG, $T(74) = -3.38$, $p < 0.05$. Furthermore, the bilateral hippocampi were connected more positively among responders, $T(74) = 3.77$, $p < 0.01$.

Seed-to-Voxel

Amygdala

Among responders the bilateral amygdalae were significantly stronger connected to three different but adjacent clusters within the occipital cortex as well as the occipitotemporal junction. The first cluster was centered within the medial occipital cortex and comprised the bilateral calcarine as well as the bilateral lingual gyri, $T(77) = 4.85$, $p < 0.001$. The two further clusters were lateralized but mirrored each other nearly congruent. Both comprised the lingual gyrus, cerebellar lobules 4 and 5 as well as parts of the fusiform gyrus, right: $T(77) = 5.27$, $p < 0.001$, left: $T(77) = 4.93$, $p < 0.001$.

Anterior cingulate cortex

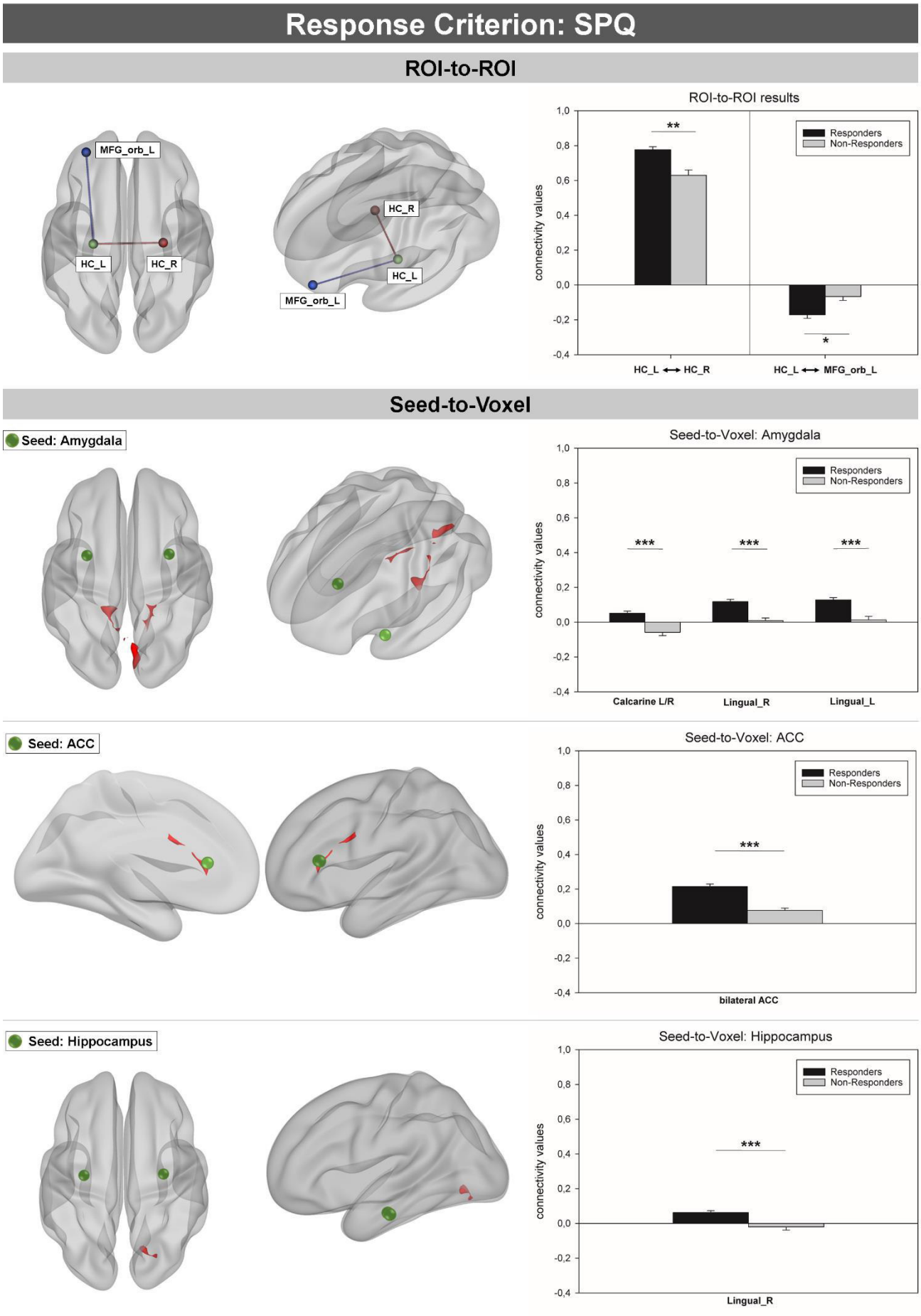
Responders exhibited significantly stronger positive connectivity between bilateral ACC seeds resulting in a cluster predominantly comprising the left anterior and mid cingulum but also small parts of the right anterior and mid cingulum, $T(77) = 6.32$, $p < 0.001$.

Hippocampus

Among Responders, the bilateral hippocampi showed significantly stronger positive connectivity with one cluster localized at the border of occipital and temporal lobe. It extended over the right lingual and fusiform gyrus but also small parts of the sixth cerebellar lobule, $T(77) = 4.00$, $p < 0.001$.

Middle frontal gyrus, pars orbitalis

No significant differences were observed regarding seed-to-voxel connectivity of the bilateral orbital parts of the MFG and whole brain voxels. The same was true when only analysing the left orbital MFG.


Response Criterion: SPQ
ROI-to-ROI
MFG_orb_L
HC_L
HC_R
HC_R
HC_L
MFG_orb_L
ROI-to-ROI results
connectivity values
Responders
Non-Responders
**
*
HC_L ↔ HC_R
HC_L ↔ MFG_orb_L
Seed-to-Voxel
Seed: Amygdala
Seed-to-Voxel: Amygdala
***
***
***
Calcarine L/R
Lingual_R
Lingual_L
Seed: ACC
Seed-to-Voxel: ACC
***
bilateral ACC
Seed: Hippocampus
Seed-to-Voxel: Hippocampus
***
Lingual_R

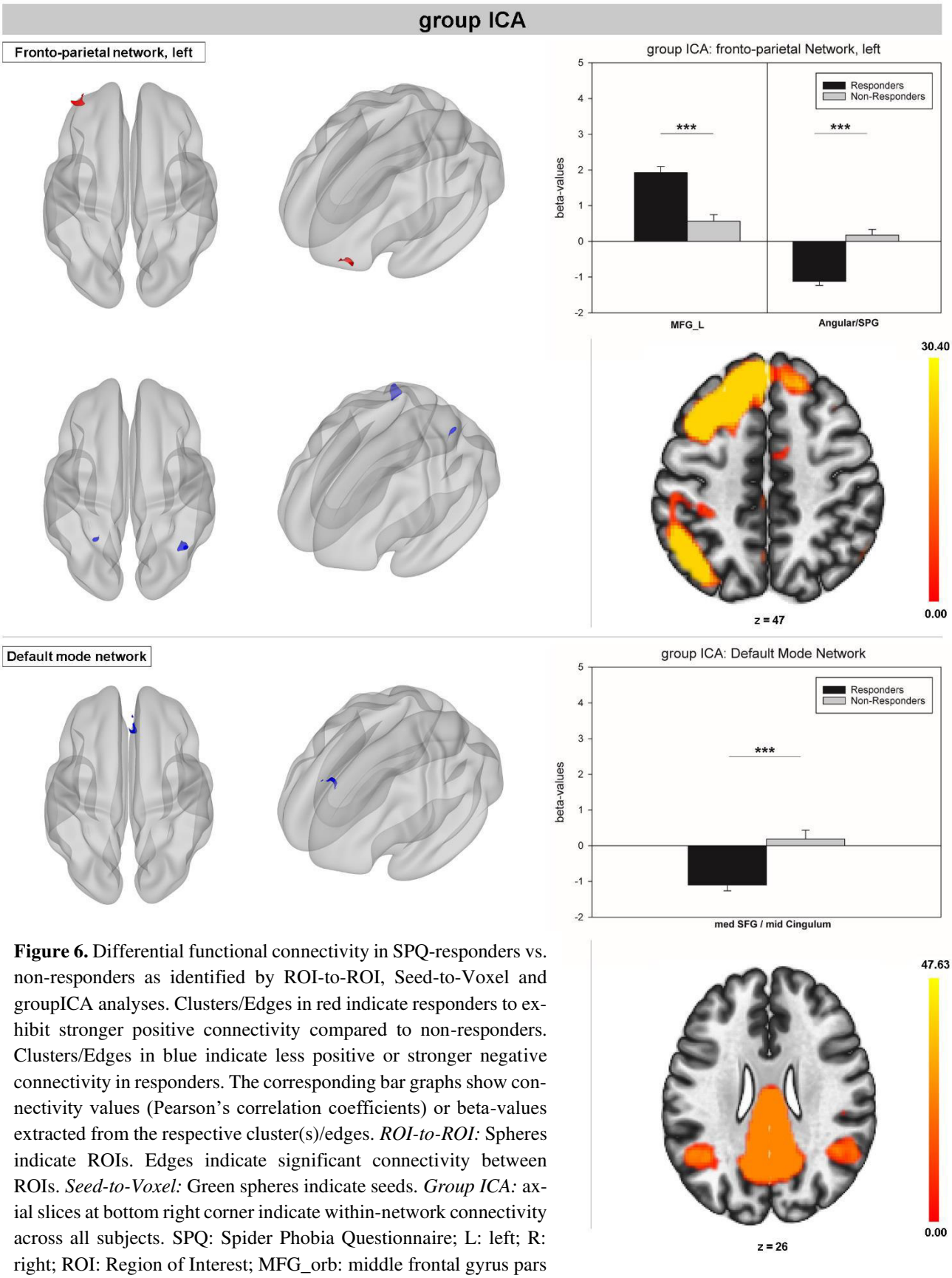


Figure 6. Differential functional connectivity in SPQ-responders vs. non-responders as identified by ROI-to-ROI, Seed-to-Voxel and groupICA analyses. Clusters/Edges in red indicate responders to exhibit stronger positive connectivity compared to non-responders. Clusters/Edges in blue indicate less positive or stronger negative connectivity in responders. The corresponding bar graphs show connectivity values (Pearson's correlation coefficients) or beta-values extracted from the respective cluster(s)/edges. *ROI-to-ROI:* Spheres indicate ROIs. Edges indicate significant connectivity between ROIs. *Seed-to-Voxel:* Green spheres indicate seeds. *Group ICA:* axial slices at bottom right corner indicate within-network connectivity across all subjects. SPQ: Spider Phobia Questionnaire; L: left; R: right; ROI: Region of Interest; MFG_orb: middle frontal gyrus pars orbitalis; HC: Hippocampus; ACC: Anterior cingulate cortex; z: reference slice MNI coordinate; MFG: middle frontal gyrus; SPG: superior parietal gyrus; SFG: superior frontal gyrus; cluster threshold: $p < 0.05$ (FDR); height-threshold: $p < 0.001$ (uncorr.); * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 10. Differential functional resting-state connectivity within SPQ-responders and non-responders (ROI-to-ROI, Seed-to-Voxel, groupICA)

ROI-to-ROI							*T*	*p* (FDR)
t-contrast: Resp > Non-Resp								
Hippocampus L	↔	Hippocampus R					3.77	< 0.01
t-contrast: Non-Resp > Resp								
Hippocampus L	↔	Inferior frontal gyrus, pars orbitalis					3.38	< 0.05

Seed-to-Voxel	Side	Voxels	x	y	z	*T*	*p* (FDR)
Amygdala							
t-contrast: Resp > Non-Resp							
Cluster 1		174	6	-88	6	4.85	< 0.001
Calcarine	R	99					
Lingual gyrus	R	46					
Lingual gyrus	L	17					
Calcarine	L	11					
AAL not-labeled	--	1					
Cluster 2		151	-10	-42	-12	5,27	< 0.001
Cerebellum 4/5	L	105					
Lingual gyrus	L	25					
Fusiform gyrus	L	14					
Vermis 4/5	--	5					
Cerebellum 3	L	2					
Cluster 3		108	16	-52	-10	4.93	< 0.001
Cerebellum 4/5	R	58					
Fusiform gyrus	R	24					
Lingual gyrus	R	17					
Cerebellum 6	R	9					
t-contrast: Non-Resp > Resp						no differential connectivity	
Anterior cingulate cortex							
t-contrast: Resp > Non-Resp							
Cluster 1		158	-14	28	10	6.32	< 0.001
Anterior cingulate cortex	L	23					
Anterior cingulate cortex	R	5					
Mid cingulate cortex	L	2					
Mid cingulate cortex	R	1					
AAL not-labeled	--	127					
t-contrast: Non-Resp > Resp						no differential connectivity	

Hippocampus							
t-contrast: Resp > Non-Resp							
Cluster 1		102	26	-78	-14	4.00	< 0.001
Lingual gyrus	R	72					
Fusiform gyrus	R	25					
Cerebellum 6	R	5					
t-contrast: Non-Resp > Resp						no differential connectivity	
Middle frontal gyrus, pars orbitalis						no differential connectivity	
group ICA	Side	Voxels	x	y	z	*T*	*p* (FDR)
Fronto-parietal network, left							
t-contrast: Resp > Non-Resp							
Cluster 1		77	-36	50	-2	5.23	< 0.001
Middle frontal gyrus, pars orb.	L	66					
Middle frontal gyrus	L	10					
Superior frontal gyrus	L	1					
t-contrast: Non-Resp > Resp							
Cluster 1		93	40	-66	42	4.29	< 0.001
Angular gyrus	R	93					
Cluster 2		59	-24	-60	52	5.50	< 0.001
Superior parietal lobule	L	53					
Middle occipital lobe	L	2					
AAL not-labeled	--	4					
Fronto-parietal network, right						no differential connectivity	
Default mode network							
t-contrast: Resp > Non-Resp						no differential connectivity	
t-contrast: Non-Resp > Resp							
Cluster 1		77	0	32	43	4.59	< 0.001
Superior frontal gyrus, medial	R	34					
Mid cingulate cortex	R	21					
Superior frontal gyrus, medial	L	19					
Mid cingulate cortex	L	3					
Salience network						no differential connectivity	

SPQ: Spider Phobia Questionnaire; ROI: Region of Interest; ICA: Independent Component Analysis; FDR: False Discovery Rate; Resp: Responders; Non-Resp: Non-Responders; L: left; R: right; AAL: Automated Anatomical Labeling Atlas; Voxels: number of voxels per cluster/region; x, y, z: MNI coordinates; $p < 0.05$ (FDR)

Group ICA

Left fronto-parietal network

Compared to non-responders, responders exhibited significantly stronger connectivity of the left middle and superior frontal gyrus with the left FPN as identified via group ICA, $T(77) = 5.23$, $p < 0.001$. Furthermore, significantly stronger negative connectivity with this network was found among responders for the right angular gyrus, $T(77) = -4.29$, $p < 0.001$, as well as left superior parietal and middle occipital gyrus, $T(77) = -5.50$, $p < 0.001$.

Default mode network

Among SPQ-responders, activity of the bilateral medial SFG as well as bilateral mid cingulate gyrus was correlated significantly more negative with the DMN than in non-responders, $T(77) = -4.59$, $p < 0.001$. No differential connectivity was observed for the right FPN as well as the SN.

4.3.3 Response criterion - BAT

Seed-to-Voxel

Amygdala

When classifying response according to the BAT as secondary outcome measure, we found activity in a cluster within the left superior and middle frontal gyrus to be stronger negatively associated with amygdala activity in responders compared to nonresponders, $T(77) = -4.91$, $p < 0.001$ (Figure 7, Table 11).

Table 11. Differential functional resting-state connectivity within BAT-responders and non-responders (ROI-to-ROI, Seed-to-Voxel, groupICA)

ROI-to-ROI						*T*	*p* (FDR)
						no differential connectivity	
Seed-to-Voxel	Side	Voxels	x	y	z	*T*	*p* (FDR)
Amygdala							
t-contrast: Resp > Non-Resp						no differential connectivity	
t-contrast: Non-Resp > Resp							
Cluster 1		88	-26	60	20	4.91	< 0.001
Superior frontal gyrus	L	67					
Middle frontal gyrus	L	21					

Anterior cingulate cortex						no differential connectivity	
Hippocampus						no differential connectivity	
Middle frontal gyrus pars orbitalis						no differential connectivity	
group ICA	Side	Voxels	x	y	z	*T*	*p* (FDR)
Fronto-parietal network, left						no differential connectivity	
Fronto-parietal network, right						no differential connectivity	
Default mode network						no differential connectivity	
Salience network						no differential connectivity	

BAT: Behavior Avoidance Test; ROI: Region of Interest; ICA: Independent Component Analysis; FDR: False Discovery Rate; Resp: Responders; Non-Resp: Non-Responders; L: left; R: right; Voxels: number of voxels per cluster/region; x, y, z: MNI coordinates; p < 0.05 (FDR)

No differential functional connectivity was observed between BAT-responders and BAT-non-responders with respect to ROI-to-ROI and groupICA analyses as well as the seeds ACC, hippocampus and MFG pars orbitalis.

4.3.4 Within-session extinction as a measure of the extinction process

ROI-to-ROI

Group comparisons of patients with high vs. low WS-ext values (see Figure 7 and Table 12) revealed significantly less negative connectivity between the right SFG and left triangular IFG in patients exhibiting more anxiety reduction during treatment, $T(77) = 4.36$, $p < 0.001$. Furthermore, connectivity of the left orbital IFG with the bilateral gyrus rectus, left: $T(77) = 3.02$, $p < 0.01$, right: $T(77) = 3.23$, $p < 0.01$, as well as the left SFG was significantly stronger within the high WS-ext group, $T(77) = 3.17$, $p < 0.01$.

Seed-to-Voxel

Amygdala

Within Seed-to-voxel analyses, the bilateral amygdalae were connected significantly less positive with the bilateral MFG as well as the left SFG in patients with high WS-ext compared to the low WS-ext group, $T(77) = -5.82$, $p < 0.001$.

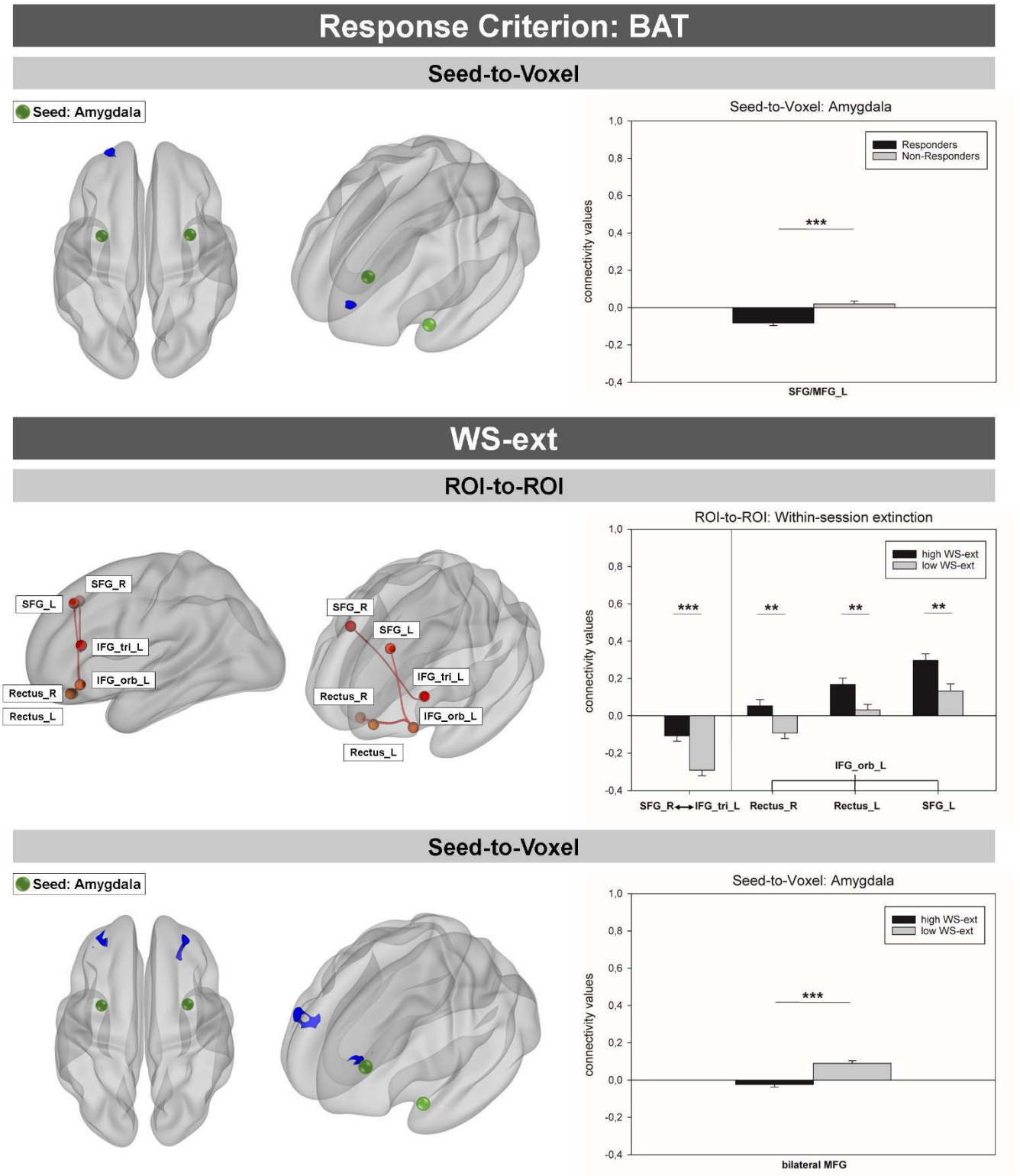


Figure 7. Differential functional connectivity in BAT-responders vs. non-responders and high WS-ext vs. low WS-ext groups as identified by ROI-to-ROI and Seed-to-Voxel analyses. Clusters/Edges in red indicate responders/high WS-ext group to exhibit stronger positive connectivity compared to non-responders/low WS-ext group. Clusters/Edges in blue indicate less positive or stronger negative connectivity in responders/high WS-ext group. The corresponding bar graphs show connectivity values (Pearson's correlation coefficients) extracted from the respective cluster(s)/edges. *ROI-to-ROI:* Spheres indicate ROIs. Edges indicate significant connectivity between ROIs. *Seed-to-Voxel:* Green spheres indicate seeds.

BAT: Behavior Avoidance Test; L: left; R: right; SFG: Superior frontal gyrus; MFG: Middle frontal gyrus; WS-ext: Within-session extinction; ROI: Region of Interest; IFG_tri: Inferior frontal gyrus, pars triangularis; IFG_orb: IFG, pars orbitalis; cluster threshold: $p < 0.05$ (FDR); height-threshold: $p < 0.001$ (uncorr.); * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 12. Differential functional resting-state connectivity within high and low WS-ext groups (ROI-to-ROI, Seed-to-Voxel, groupICA)

ROI-to-ROI			*T*	*p* (FDR)
t-contrast: high WS-ext > low WS-ext				
Superior frontal gyrus R	↔	Inferior frontal gyrus, triangularis L	4.36	< 0.001
Rectus R	↔	Inferior frontal gyrus, pars orbitalis L	3.23	< 0.01
Rectus L	↔	Inferior frontal gyrus, pars orbitalis L	3.02	< 0.01
Superior frontal gyrus L	↔	Inferior frontal gyrus, pars orbitalis L	3.17	< 0.01
t-contrast: low WS-ext > high WS-ext			no differential connectivity	

Seed-to-Voxel	Side	Voxels	x	y	z	*T*	*p* (FDR)
Amygdala							
t-contrast: high WS-ext > low WS-ext						no differential connectivity	
t-contrast: low WS-ext > high WS-ext							
Cluster 1		166	26	34	22	5.57	< 0.001
Middle frontal gyrus	R	117					
AAL not-labeled	--	49					
Cluster 2		115	-28	48	22	4.64	< 0.001
Middle frontal gyrus	L	109					
Superior frontal gyrus	L	6					
Anterior cingulate cortex						no differential connectivity	
Hippocampus						no differential connectivity	
Middle frontal gyrus, pars orbitalis						no differential connectivity	

group ICA	Side	Voxels	x	y	z	*T*	*p* (FDR)
Fronto-parietal network, left						no differential connectivity	
Fronto-parietal network, right						no differential connectivity	
Default mode network						no differential connectivity	
Salience network						no differential connectivity	

WS-ext: Within-session extinction; ROI: Region of Interest; ICA: Independent Component Analysis; FDR: False Discovery Rate; high WS-ext: group with high WS-ext values according to median split; low WS-ext: group with low WS-ext values according to median split; L: left; R: right; AAL: Automated Anatomical Labeling Atlas; Voxels: number of voxels per cluster/region; x, y, z: MNI coordinates; $p < 0.05$ (FDR)

4.4 Discussion

Especially within mental health, pre-treatment moderators of response are of major interest as they might aid in the development of personalized treatments and can thus serve to improve response rates (Lueken & Hahn, 2016; Lueken et al., 2016). The aim of the present investigation was to identify pre-treatment resting-state connectivity signatures that moderate treatment response in specific phobia. Main findings were: a) prior to treatment, responders exhibited stronger inhibitory fronto-limbic connectivity compared to non-responders, which was also reflected in altered ECN and DMN connectivity between responders and non-responders; b) furthermore, SPQ responders were characterized by heightened connectivity between the amygdala and brain regions related to the ventral visual pathway; c) when using the BAT as classification criterion, again stronger inhibitory connectivity of the amygdala with orbitofrontal structures was observed among responders; d) similar results were found when comparing patients with high and low WS-ext values. Furthermore, ROI-to-ROI analyses revealed stronger positive connectivity within the PFC among patients exhibiting high WS-ext.

In line with our hypothesis, we observed responders to exhibit stronger inhibitory fronto-limbic connectivity between left hippocampus and left orbital MFG within ROI-to-ROI analyses. Moreover, bilateral hippocampi were connected significantly more positive among responders. Those results can be interpreted with respect to hippocampal replay, which has been suggested to be involved in rumination and worry in anxiety disorders and depression (Heller & Bagot, 2020). It is defined as “the rapid, coordinated reactivation of encoding-activated cellular ensembles during sleep and resting wakefulness” (Heller & Bagot, 2020, p. 431) and has been associated with retrieval of (fear) memory contents in rodents as well as humans (Schapiro, McDevitt, Rogers, Mednick, & Norman, 2018; Schuck & Niv, 2019; Staresina, Alink, Kriegeskorte, & Henson, 2013; Wu, Haggerty, Kemere, & Ji, 2017). The connection between hippocampus and PFC seems to be especially relevant in memory-guided behavior based on hippocampal replay (Zielinski, Tang, & Jadhav, 2020) as the inhibition of ventral hippocampal projections to the medial PFC via an optogenetic approach leads to a disruption of anxiety and avoidance behavior in rodents (Padilla-Coreano et al., 2016). In contrast, an increase of synchrony between hippocampus and medial PFC has been observed during states of anxiety (Lesting et al., 2011). Our ROI-to-ROI results might therefore indicate a reduced retrieval of fear-relevant memory contents among responders. This may support the acquisition of the new fear-inhibitory memory trace or facilitate its competition with the old fear-related

memory trace thus resulting in enhanced response. Hippocampal replay can also explain the observed stronger connectivity within bilateral hippocampi among responders. Padilla-Coreano et al. (2016) only found bilateral but not unilateral inhibition of the hippocampus-PFC synchrony to alter physiological correlates of anxiety within the basolateral amygdala.

Deduced from those results and to further examine the hypothesized mechanism of inhibitory connectivity between frontal and limbic structures, we introduced the orbital MFG as seed. Regardless of the previous ROI-to-ROI results, we were not able to confirm the findings in the seed-to-voxel analysis. We presume this to be due to FDR-correction for multiple comparisons resulting in more conservative thresholding in seed-to-voxel compared to ROI-to-ROI analyses. Possibly, the negative correlation between orbital MFG and hippocampal activity can be confirmed in future studies with increased sample sizes.

As for the SPQ, we expected to detect stronger inhibitory connectivity with the frontal cortex among BAT-responders as well. Indeed, we observed stronger inhibitory seed-to-voxel connectivity between amygdala and left superior as well as middle frontal gyrus within BAT-responders compared to non-responders. This is in line with ROI-to-ROI results of the SPQ and further supports our hypothesis of pronounced inhibitory connectivity in responders.

Similarly, we hypothesized inhibitory seed-to-voxel connectivity of the amygdala with the PFC to be pronounced in SPQ-responders as well. Furthermore, we expected it to be stronger connected to the ACC among responders (Klumpp, Keutmann, Fitzgerald, Shankman, & Phan, 2014). In contrast to our hypotheses, we found the amygdala to exhibit significantly stronger positive connectivity with three clusters in the occipital and posterior temporal lobe, which followed the bilateral ventral visual pathway (DeYoe, Felleman, Van Essen, & McClendon, 1994; Gilbert, 2013). Enhanced connectivity in responders might indicate facilitated input of visual information to the amygdala, which may subsequently promote the formation of stronger fear-inhibitory memory traces. However, also the opposite directionality is possible. This interpretation is supported by previous findings on backward connections of the amygdala to visual cortices, which are thought to account for saliency of emotional visual information (Catani, Jones, Donato, & Ffytche, 2003; Furl, Henson, Friston, & Calder, 2013; Lim, Padmala, & Pessoa, 2009; Morris et al., 1998; Vuilleumier & Pourtois, 2007; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004) and have been observed within non-human primates as well (Amaral, Behniea, & Kelly, 2003). Within this framework, our results suggest responders to be characterized by pronounced amygdala-driven processing of fear-relevant

stimuli within the visual cortex. Together with the described inhibitory fronto-limbic connectivity, this might be beneficial within extinction training as salient aversive stimuli are preferentially processed but also accompanied by emotional regulation. Correspondingly, recent research on attentional biases towards threat stresses the lack of executive control as primary attentional deficit in anxiety (McNally, 2019).

The results with respect to the amygdala are in line with those obtained for the hippocampus, which was introduced as additional seed after ROI-to-ROI analysis. Again, we originally hypothesized the hippocampus to be more inhibitorily connected to prefrontal structures in responders. However, we found it to be significantly more positively connected to the ventral visual pathway in responders as it was demonstrated for the amygdala. Amygdala and hippocampus are known to be connected (Papez, 1937; Sheline, Price, Yan, & Mintun, 2010) and the ventral visual pathway also represents a link between visual cortex and hippocampus (Miyashita, 1993). This might be the reason for the overlapping findings between seed-to-voxel analyses of the amygdala and hippocampus. The results regarding the hippocampus again support the interpretation that was set up within the previous paragraph: responders seem to be characterized by heightened visuo-limbic connectivity on the one hand, which may facilitate information processing within fear-relevant structures and stronger inhibitory fronto-limbic connectivity on the other hand, which may lead to attenuated fear memory retrieval. More recent findings by Nawa and Ando (2019) on effective connectivity between amygdala, hippocampus and VMPFC provide further support for this interpretation and highlight the relevance of the interplay of those three structures with respect to the elaboration and retrieval of autobiographical memories. Hippocampus - VMPFC connectivity was increased when reliving emotionally arousing events (Nawa & Ando, 2019).

To directly address the extinction process during exposure itself, we exploratively introduced WS-ext as a process measure of inhibitory learning. Within ROI-to-ROI analyses, we expected to detect stronger inhibitory fronto-limbic connectivity in patients exhibiting high WS-ext compared to low WS-ext patients as it was observed within SPQ-responders and non-responders. However, this was not the case. Instead, we found dorsolateral and ventromedial prefrontal cortices to be stronger connected to the orbital IFG in high WS-ext patients compared to low WS-ext patients. Furthermore, the right SFG was connected less inhibitorily to the triangular IFG in patients who reported a stronger reduction of anxiety during exposure. Even though we did not observe the expected inhibitory fronto-limbic connectivity within the high

WS-ext patients, the results do not contradict this hypothesis. Repeatedly, dorsolateral, ventrolateral and ventromedial prefrontal areas have been referred to as neural substrates of anxiety disorders and fear extinction (Fullana et al., 2016; Quirk & Mueller, 2008; Sehlmeyer et al., 2009; Shin & Liberzon, 2010). Besides, anxiety disorder pathology, the VMPFC is thought to be involved in automatic emotion regulation, whereas the DLPFC and VLPFC were related to voluntary emotion regulation (Golkar et al., 2012; Phillips, Ladouceur, & Drevets, 2008). Furthermore, the VLPFC has been suggested to account for the evaluation of salience as well as the need for regulation (Kohn et al., 2014). According to the extended process model of emotion regulation (Sheppes, Suri, & Gross, 2015), those structures might represent the three steps of (voluntary) emotion regulation: the evaluation of the need to regulate (VLPFC) and the selection of an adequate strategy as well as their implementation (DLPFC). Heightened connectivity between those regions might therefore reflect enhanced reconciliation and balancing of those processes, which may in turn facilitate extinction during subsequent exposure (Delgado, Nearing, LeDoux, & Phelps, 2008; Zilverstand, Parvaz, & Goldstein, 2017).

Seed-to-voxel analyses of the amygdala comparing high and low WS-ext groups revealed significant differential connectivity with the bilateral MFG as it was identified within the same analysis among BAT responders and non-responders. However, when considering the absolute connectivity values, we found high WS-ext patients to exhibit less positive connectivity of amygdala and MFG compared to low WS-ext patients. Therefore, the results cannot be interpreted in terms of inhibitory connectivity. Instead, stronger connectivity between amygdala and MFG within the low WS-ext group potentially indicates a heightened need for regulatory control within the low WS-ext group. The finding needs further investigation.

With respect to connectivity within large scale networks, we expected responders to exhibit less pathology in terms of previously demonstrated alterations in anxiety disorders. We obtained corresponding results with respect to the left FPN (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008), which is also referred to as the ECN (Seeley et al., 2007). We found enhanced participation of the left MFG with respect to responders compared to non-responders. On the other hand, the right angular gyrus and parts of the superior parietal lobule were correlated significantly less with the network among responders. In general, the FPN/ECN is thought to be involved in top-down control (Dosenbach et al., 2008; Sylvester et al., 2012). With respect to anxiety disorders, decreased functioning of the FPN has been reported (Sylvester et al., 2012). Transferred to the current results, the increased participation of the left MFG within the

FPN in responders possibly indicates stronger emotion regulation capabilities in responders already prior to treatment, which facilitate subsequent inhibitory learning.

Correspondingly, we hypothesized responders to exhibit less DMN pathology in terms of an anterior-posterior dissociation (heightened connectivity of the frontal portions vs. decreased connectivity of the posterior portions) as it was previously shown to characterize anxiety disorders (Coutinho et al., 2016; Lai & Wu, 2014; Liao et al., 2010; Sylvester et al., 2012; Zhao et al., 2007). We found the medial SFG to participate significantly less in DMN processes within SPQ-responders thus confirming the hypothesis. As the DMN dissociation has been suggested to constitute a neural correlate of excessive rumination in anxiety disorder patients (Coutinho et al., 2016), attenuated participation of the medial SFG within the DMN of responders may reflect less anxiety-related rumination, which in turn facilitates emotion regulation via structures related to the FPN or ECN.

We further expected to detect heightened participation of the ACC within the SN of responders. However, no significant differences in ACC participation within the SN were observed. Even though SN alterations have been demonstrated in anxiety disorders (Xu et al., 2019), its intrinsic pre-treatment connectivity does not seem to moderate response according to our results. However, we found differences between responders and non-responders in ACC connectivity within seed-to-voxel analyses. Bilateral ACCs and mid cingulate cortices were stronger interconnected within SPQ-responders. This was not in line with our hypothesis of pronounced ACC-amygdala connectivity as demonstrated to be predictive for treatment outcome in SAD patients (Klumpp et al., 2014; Lueken et al., 2016). Nevertheless, increased resting-state connectivity of the ACC across hemispheres might point to increased preparation for upcoming events (Brown & Braver, 2007; Stoeckel, Esser, Gamer, Büchel, & von Leupoldt, 2016), which may promote the subsequent recruitment of brain activity to cope with this risk. However, this interpretation remains speculative and needs further investigation.

When comparing the observed results of the two response criteria as well as the WS-ext results, there is an overlap with respect to inhibitory fronto-limbic connectivity, which seems to characterize responders and high WS-ext patients. However, results also differ substantially between the three classification methods. For the BAT, no further results have been observed, neither for the seeds hippocampus, ACC, or MFG nor regarding ROI-to-ROI analyses or group ICA of the FPN, DMN, and SN. Except for the ROI-to-ROI analyses, the same is true for the WS-ext analyses. As baseline SPQ and BAT as well as reductions from pre to post were significantly correlated (SPQ/BAT: $r = .382$, $p < 0.01$; ΔSPQ/ΔBAT: $r = .482$, $p < 0.001$) we expected

to detect similar results regarding the classification methods. In contrast to the SPQ, the BAT is a behavioral measure, which might be closer to the underlying pathomechanism of avoidance and inhibitory learning. Therefore, inhibitory fronto-limbic connectivity might be especially relevant for BAT response, thus leading to the circumscribed results with respect to amygdala – SFG/MFG connectivity. As SPQ and BAT groups overlap for only about 61.22%, also differences in group composition might have led to divergent results when varying response classification methods. The differing results with respect to the WS-ext groups might again be due to the different composition of the groups. As for the comparison of SPQ and BAT classification, high WS-ext patients are not necessarily classified as BAT or SPQ-responders and vice versa. The overlap is even smaller with the WS-ext groups. This points to different aspects of extinction and response being covered by the three classification methods. Furthermore, the relation of WS-ext and treatment response has been questioned frequently and there are opposing results on its predictive value regarding treatment outcome (Craske et al., 2008). However, within the present investigation the amount of SPQ reduction was significantly correlated with the amount of WS-ext values (ΔSPQ/WS-ext: $r = .231$, $p < 0.05$) thus indicating treatment response and WS-ext to be interrelated. Regardless of this still ongoing discussion, the differing results with respect to SPQ- and BAT-based response classification as well as WS-ext crucially need replication. Future studies should try to further investigate the differences between classification methods and combine them to achieve a more comprehensive understanding of the individual aspects covered by the different methods (Loerinc et al., 2015).

Limitations

The present investigation was based on a very selective sample of patients due to the strict in- and exclusion criteria. On the one hand, this leads to high internal validity and enables the precise investigation of connectivity signatures as moderators of treatment outcome. On the other hand, generalizability of our findings towards samples from clinical practice as well as variability in potential moderators besides connectivity (e.g. comorbidity) is restricted.

Generalizability of our results may be limited to a certain extent due to the use of VRET, too. We chose to use VR technology within our study as it allows for high experimental control and standardization, which is advantageous with respect to comparability of subjects and enabled us to minimize interindividual differences in response caused by variability in the execution of exposure. Furthermore, VRET allowed for the application of the very same dose of

exposure for every patient. However, VRET also represents a specific form of psychotherapy, which involves characteristics (e.g. disconfirmation of certain beliefs is not possible in VR) that might also condense within treatment response and the associated pre-treatment characteristics and restrict individualization of exposure. Nevertheless, individualization is probably less relevant in specific phobia compared to other anxiety disorders and VRET has been shown to mirror a variety of traditional CBT features (Bouchard et al., 2017; Carl et al., 2019; Powers & Emmelkamp, 2008; Valmaggia et al., 2016). Furthermore, it relies on the same mechanism of action and has been demonstrated to be equally effective (Wechsler et al., 2019). Therefore, we believe that potential differences due to the use of VRET do not impair the transfer of our findings towards traditional exposure-based CBT substantially. Nevertheless, we recommend the replication of our findings within future studies involving exposure to real spiders.

Due to the investigation of response, the present study was restricted to a dichotomous approach of comparing responders and non-responders. We chose to analyze our data in this dichotomous way due to the long-term goal of identifying pre-treatment characteristics that guide clinical decision-making, which is an inherently dichotomous task. Another methodological limitation of the present investigation is related to the type of connectivity assessed. Functional connectivity does not necessarily reflect the existence of a direct structural equivalent. However, it was shown to be substantially constrained by underlying structural connections (Greicius, Supekar, Menon, & Dougherty, 2009; Van Dijk et al., 2010). Advancements in methodology possibly allow for further clarifying the relationship of structural and functional connectivity in the future (Damoiseaux & Greicius, 2009). Furthermore, functional connectivity does not allow inference of causal directionality. Therefore, functional connectivity results have to be interpreted carefully when referring to their underlying neural function. However, methods like dynamic causal modeling (DCM) can be used to test for causal hypotheses and thus also directionality of connectivity (Friston, Harrison, & Penny, 2003).

Finally, the present pre-post design leaves us with the question whether the same connectivity signatures also moderate treatment outcome over a longer period of time after exposure. This can be tested via the analysis of follow-up data, which have not been included in the present investigation. Furthermore, replication is necessary within other anxiety disorders and with respect to treatments that extend beyond the setting of a one-session exposure.

Outlook

As the present investigation is part of a bicentric study on response to exposure treatment, replication within a second, independent sample will be the next step of data analysis. Both sites have recruited a sample of 87 spider phobic patients, which were treated in a highly standardized manner to ensure comparability of sites. Therefore, the Münster sample represents the ideal basis for replication of our findings. Furthermore, assessment of connectivity signatures moderating pre - follow-up outcome is planned. Future studies should also try to translate our findings to other anxiety disorders and therapeutic settings.

Besides replication across sites and timepoints, the use of graph theory might open up the possibility of gathering further information on network arrangements and the overall structure of the brain's networks (Bassett & Sporns, 2017; Bullmore & Sporns, 2009; Van Den Heuvel & Pol, 2010). Those graphs can be analyzed with respect to a variety of features e.g. path length, clustering coefficient, centrality and modularity (Van Den Heuvel & Pol, 2010). Responders and non-responders might also differ with respect to such features. Furthermore, analyzing functional network connectivity (FNC) might be a promising approach as well. It is concerned with connectivity between functional networks (Jafri, Pearlson, Stevens, & Calhoun, 2008). Within the present investigation, we focused on exploring differences within brain networks like the FPN or DMN. For example, responders might be characterized by heightened connectivity between AN and DMN as well as ECN, which have been identified to be hypoconnected in anxiety disorders (Xu et al., 2019).

Our present results also provide initial starting points for treatment adaptations with the goal to enhance treatment outcome for non-responders as well. Based on our current findings, such adaptations need to support inhibitory fronto-limbic connectivity. This might be achieved e.g. via the implementation of an emotion regulation training prior to treatment (see e.g. Goldin & Gross, 2010; Neacsiu, Eberle, Kramer, Wiesmann, & Linehan, 2014). On the other hand, studies have already shown neurofeedback to be a promising tool for enhancing emotion regulation and fronto-limbic associations in particular (Brühl, Scherpiet, et al., 2014; Lorenzetti et al., 2018; Zotev, Phillips, Young, Drevets, & Bodurka, 2013). Besides emotion regulation training and neurofeedback, also pharmacological approaches may be effective in enhancing inhibitory fronto-limbic connectivity. Promising approaches may be the application of gamma-amino butyric acid (GABA) related drugs, which are currently predominantly applied within

the treatment of epilepsy. GABA seems to alter resting-state connectivity and enhances cognitive control (Haag et al., 2015). In line with this finding, valproate and pregabalin have been demonstrated to have anxiolytic effects (Bach, Korn, Vunder, & Bantel, 2018). Moreover, yohimbine is discussed as potentially enhancing cognitive control and exposure treatment (Powers, Smits, Otto, Sanders, & Emmelkamp, 2009). However, the results are still inconclusive (Meyerbröker, Morina, & Emmelkamp, 2018; Tuerk et al., 2018). Third, transcranial magnetic stimulation (TMS) may constitute an option for directly manipulating brain activity and thus also connectivity. This is especially interesting with respect to our results as the frontal regions that are inhibitorily connected to defensive system structures in responders are situated within the lateral orbitofrontal cortex and DLPFC, which can be reached easily with the TMS coil. Preliminary findings suggest repetitive TMS to be beneficial for extinction in non-clinical samples (Herrmann, 2019; Raij et al., 2018) but also for exposure in anxiety disorders (Greenberg, 2007). Similar results exist for the application of transcranial direct-current stimulation (tDCS; Herrmann, 2019), which may also serve to directly manipulate brain activity and seems to support extinction in non-clinical samples (Dittert, Hüttner, Polak, & Herrmann, 2018) as well as in anxiety disorder patients (D'Urso, Mantovani, Patti, Toscano, & de Bartolomeis, 2018; Kekic, Boysen, Campbell, & Schmidt, 2016).

4.5 Conclusion

In the present investigation, we were able to identify inhibitory fronto-limbic connectivity as moderator of response to exposure-based CBT in specific phobia. Moreover, pronounced visuo-limbic connectivity seems to characterize responders. During exposure, stronger excitatory connectivity between dorsolateral, ventrolateral and ventromedial PFC seems to promote within-session extinction. Those three patient features may lead to a facilitation of fear extinction via inhibitory learning and thus enhanced treatment outcome. In contrast, absence of those connectivity features seems to impede exposure from acting. Our results provide starting points for treatment adaptations that may lead to enhanced outcome within patients that are currently classified as non-responders. Based on our findings, methods that support inhibitory fronto-limbic connectivity prior to treatment may prepare the neural soil for inhibitory learning to yield fruit. Possibly, this can be achieved via the training of emotion regulation capacities prior to treatment, the supplemental application of special psychotropic drugs or the use of non-

invasive brain stimulation techniques like TMS or tDCS. Future studies should further investigate neural pre-treatment characteristics that relate to response and test treatment adaptations to increase response according to different patient groups and treatment modalities. This might help to optimally exploit the strengths of exposure treatment in a larger group of anxiety disorder patients.

5 Discussion: Pre-treatment moderators of inhibitory learning

The induction of fear extinction via inhibitory learning is considered the underlying mechanism of action in exposure treatment, which is the key module of CBT in anxiety disorders (Craske et al., 2017). Due to roughly one-hundred years of research on fear conditioning and extinction in humans and animals as well as the successful translation of findings into clinical practice, the understanding of the mechanisms of action of exposure-based CBT for anxiety disorders is unequalled in mental health (Sewart & Craske, 2020). This thesis aimed at further extending this knowledge by investigating two main research questions with respect to moderators of inhibitory learning during exposure treatment: first, we asked whether secondary SAD moderates the neural substrates as well as treatment outcome of primary PD/AG. Second, we aimed at investigating differences in pre-treatment resting-state functional connectivity signatures between spider phobia patients responding to exposure based-treatment and those who remain as non-responders. Main findings were: PD/AG-specific treatment bears potential to generalize to secondary SAD symptomatology, thus favouring the idea of a general mechanism that may support the transfer of inhibitory learning experiences. Neurally, secondary SAD was accompanied by a specific signature within the ventral visual pathway, which was attenuated to the level of PD/AG patients without comorbid SAD after treatment. The second study revealed pronounced inhibitory fronto-limbic as well as enhanced visuo-limbic connectivity to characterize spider phobia patients responding to exposure-based treatment. The visuo-limbic connectivity was represented by stronger positive connectivity of the bilateral amygdalae with regions of the bilateral ventral visual pathway. Furthermore, dorsolateral and ventromedial PFC were stronger connected to the VLPFC in patients exhibiting high WS-ext.

5.1 Evidence for three moderating functional systems

Our results provide evidence for three functional systems moderating inhibitory learning in anxiety disorders: first, inhibitory fronto-limbic connectivity seems to moderate treatment outcome. Across different analyses, this was especially true for the MFG, which was stronger inhibitorily connected to the hippocampus as well as the amygdala in responders and participated more within the ECN among those patients. With respect to the hippocampus, it may

indicate a reduced retrieval of fear-relevant memory contents among responders (Heller & Bagot, 2020), which possibly supports the acquisition of the new fear-inhibitory memory trace or facilitates its competition with the old fear-related memory trace. Overall, the results suggest executive control to be stronger in patients exhibiting pronounced inhibitory fronto-limbic connectivity. This is in line with animal (Milad & Quirk, 2012; Myers & Davis, 2007; Sotres-Bayon & Quirk, 2010) as well as human research on fear extinction (Greco & Liberzon, 2015; Quirk & Mueller, 2008; Vervliet et al., 2013), which suggests the amygdala, hippocampus and PFC to be important structures in the extinction process and implicates their interplay to be highly relevant for the formation of the new inhibitory memory trace as well as extinction recall.

Second, we found heightened intrinsic connectivity within the PFC among patients, exhibiting more WS-ext. The DLPFC and VMPFC were stronger connected to the VLPFC compared to low WS-ext patients. Within animal as well as human studies, the VMPFC has been frequently demonstrated to play an important role in fear extinction (Milad & Quirk, 2012; Vervliet et al., 2013). It is suggested to inhibit the amygdala and thus fear responses (Milad & Quirk, 2012; Vervliet et al., 2013). Across species it is further thought to account for (automatic) emotion regulation processes (Golkar et al., 2012; Phillips et al., 2008; Quirk & Beer, 2006), which are known to contribute to the etiology, maintenance and treatment of anxiety disorders (Cisler & Olatunji, 2012). In contrast, the VLPFC was suggested to account for the evaluation of the need for emotion regulation (Kohn et al., 2014). Via the VMPFC it seems to be involved in fear extinction as well (Delgado et al., 2008). The DLPFC is suggested to account for cognitive emotion regulation (Hartley & Phelps, 2010) and the voluntary selection and implementation of an adequate strategy (Sheppes et al., 2015; Zilverstand, Parvaz, et al., 2017). Both, VLPFC and DLPFC can thus be related to voluntary and cognitive emotion regulation (Golkar et al., 2012; Phillips et al., 2008). Heightened connectivity between VLPFC, DLPFC, and VMPFC suggests enhanced reconciliation and balancing of the different emotion regulation processes, which may enhance fear extinction (Hartley & Phelps, 2010; Quirk & Beer, 2006; Zilverstand, Parvaz, et al., 2017).

Third, we found regions related to the processing and transfer of visual information to play an important role with respect to exposure. Results of both presented studies overlap with respect to the involvement of the ventral visual pathway. However, the nature of involvement varied between studies. Within the first study, SAD comorbidity moderated the neural signatures of PD/AG in terms of heightened activity within the ventral visual pathway during a task-fMRI investigation, whereas in the second study heightened resting-state connectivity of those

regions with the amygdala was shown to moderate treatment response. Nevertheless, the two-fold appearance of the ventral visual pathway in both studies, which addressed different anxiety disorders, points to its importance within exposure treatment. In general, the pathway is considered to be involved in the transfer of visual information from the primary visual cortex (V1) via V2, V4 and the inferior temporal lobe to the temporal pole including the amygdala (Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003; Williams et al., 2006). Thus, it is part of LeDoux's high road (LeDoux, 1996). Furthermore, it has been shown to be highly relevant in object recognition and was described in humans as well as animals (Gilbert, 2013; McDonald, 1998).

In our study on PD/AG and secondary SAD, we interpreted the heightened activation within the ventral visual pathway as pathophysiological feature of comorbid SAD, which indicates exaggerated processing of visually salient cues. Enhanced visual attention to threat-relevant information has been frequently observed in anxiety disorders (Cisler & Koster, 2010; McNally, 2019; Michalowski et al., 2009; Mueller et al., 2009; Weymar, Keil, & Hamm, 2014). Correspondingly, enhanced activation of visual processing areas like the primary and secondary visual cortex as well as the ventral visual pathway has been demonstrated as a (functional and structural) pathophysiological characteristic of SAD (Brühl, Delsignore, et al., 2014; Etkin & Wager, 2007; Frick et al., 2014) and specific phobia (Åhs et al., 2009; Del Casale et al., 2012; Ipser et al., 2013; Lange et al., 2019; Lueken et al., 2011; Peñate et al., 2017). This is also reflected in heightened task-based connectivity of visual processing regions like the fusiform gyrus, inferior temporal cortex, and inferior occipital cortex with the amygdala, which has been shown in SAD (Frick, Howner, Fischer, Kristiansson, & Furmark, 2013; Jung et al., 2018; Liao et al., 2011) and specific phobia patients (see positron-emission-tomography study by Åhs et al., 2009). However, visual processing regions have not only been implicated in the pathophysiology of anxiety disorders. They have also been directly related to treatment outcome and were shown to have predictive value (Lueken et al., 2016; Marwood et al., 2018; Santos et al., 2019). The task fMRI results of Doehrmann et al. (2013) and connectivity analyses of Whitfield-Gabrieli et al. (2016) point to decreased pre-treatment activation in visual processing regions as well as decreased connectivity with the amygdala to be beneficial with respect to treatment outcome. In contrast, the three meta-analyses of Lueken et al. (2016), Marwood et al. (2018), and Santos et al. (2019) have demonstrated heightened activation within those regions to be predictive of more symptomatic improvement in anxiety disorders. This is in line with findings of Niles, Mesri, Burklund, Lieberman, & Craske (2013), Barry, Sewart, Arch, & Craske (2015), and Barry, Vervliet, & Hermans (2015), who demonstrated the attentional bias to moderate

CBT treatment outcome. Slower disengagement from threat – and thus stronger attentional bias towards threat – was related to more symptomatic improvement. This might be due to heightened attentional focusing on the CS to promote disconfirmation of beliefs (i.e. prediction error) and thus fear extinction (Craske, Hermans, & Vervliet, 2018).

Taken together, fMRI-findings in SAD and specific phobia as well as other anxiety disorders suggest pronounced visual processing as pathophysiological characteristic of anxiety disorders. Additionally, meta-analytic literature as well as our findings within both presented studies point to pronounced visual processing prior to treatment being beneficial with respect to treatment outcome. At first glance, those results might seem to be contradictory as heightened activity within regions related to the pathophysiology may suggest heightened severity and thus worse treatment outcome. However, heightened activation within visual processing regions might be due to those patients exhibiting less (attentional) avoidance behavior, which is highly beneficial for exposure treatment.

5.2 Working model

Within the following paragraphs, the three functional systems should be integrated in a hypothetical working model of pre-treatment neural signatures moderating inhibitory learning in anxiety disorder patients (Figure 8). It refers to the functional systems and connectivity observed in responders and high WS-ext patients and thus represents a model of beneficial preconditions for exposure treatment. The model description includes hypothesized directionality of influences between the systems and should provide starting points for future research questions.

According to the model of LeDoux (LeDoux, 1996; LeDoux, 2000), the pathological CS-US association is formed within the amygdala, which receives sensory inputs on (potentially threatening) environmental stimuli via the high and low road. Once an anxiety disorder has evolved, the amygdala together with the defensive system network are hyperactive in response to threatening stimuli (Fanselow, 1994; Sehlmeyer et al., 2009; Shin & Liberzon, 2010). This has been related to hypervigilance towards the CS (Cisler & Koster, 2010), which was demonstrated as pathological characteristic across the whole spectrum of anxiety disorders (Cisler & Koster, 2010; Kimble et al., 2014; McNally, 2019). Neurally, hypervigilance is thought to be mediated by back-projections from the amygdala to the visual cortex (Furl et al.,

2013; Vuilleumier & Pourtois, 2007; Vuilleumier et al., 2004). Via those projections, the amygdala signals the visual cortex to preferentially process certain stimuli (Vuilleumier et al., 2004) as they e.g. signal threat. Structurally, those back-projections are thought to be represented by the ventral visual pathway, which bidirectionally connects visual cortex and anterior temporal lobe (Catani et al., 2003).

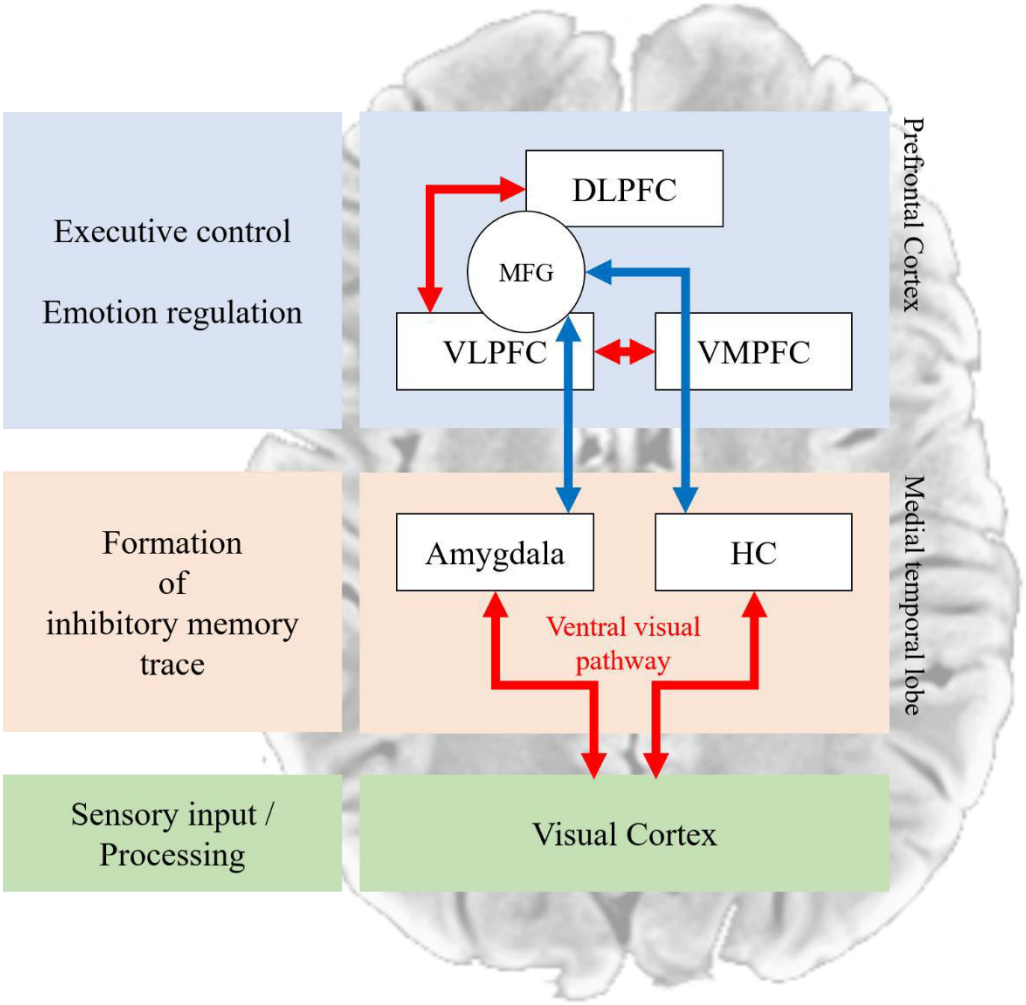


Figure 8. Working model of moderators of inhibitory learning. Arrows in red indicate positive connectivity, arrows in blue indicate inhibitory connectivity between brain regions. DLPFC: Dorsolateral prefrontal cortex; VLPFC: Ventrolateral prefrontal cortex; VMPFC: Ventromedial prefrontal cortex; HC: Hippocampus.

Consequently, it is not surprising that the existence of a secondary anxiety disorder leads to even pronounced activation within this pathway prior to treatment (Seeger et al., 2019). However, this additional activation within the ventral visual pathway was attenuated to the level of

patients without comorbidity after treatment and thus did not impede extinction and in consequence treatment outcome of the primary disorder. Instead, our results point to enhanced visuolimbic connectivity being beneficial for exposure. Ventral visual pathway activation thus represents a pathophysiological feature of anxiety disorders, which is even pronounced if comorbid anxiety disorders are present. Furthermore, it seems to be relevant for successful treatment as it was previously demonstrated within several meta-analyses (Lueken et al., 2016; Marwood et al., 2018; Santos et al., 2019). This is further supported by findings on the attentional bias towards threat, which seems to be beneficial for exposure outcome as it enhances the prediction error and thus inhibitory learning (Barry et al., 2015; Craske et al., 2018; Niles et al., 2013). One can hypothesize the differential relevance of visual processing areas to be due to heightened conditionability, which has been demonstrated for anxiety disorders (Orr et al., 2000). On the one hand, heightened conditionability might lead to facilitated acquisition of pathological CS-US associations, which may in turn result in the pathophysiological hyperactivation of the amygdala, the defensive system network, the ventral visual pathway and visual cortices (pathophysiological feature). On the other hand, heightened conditionability may facilitate the formation of the new fear-inhibitory memory trace as well (treatment-supporting feature).

According to the model of Craske et al. (2012), the new memory trace, which was established via extinction during exposure needs to compete with the old fear-related memory trace. The instance, which is thought to be responsible for the inhibition of the old memory trace during extinction training as well as extinction recall is the PFC (Knight et al., 2004; Quirk & Mueller, 2008; Vervliet et al., 2013). Furthermore, amygdala and hippocampus play an important role in human fear extinction (Greco & Liberzon, 2015; Maren, 2008; Vervliet et al., 2013). This is where the two other systems, which were shown to moderate inhibitory learning within the presented analyses, come into play. Via extinction, regulatory control of the PFC over limbic regions involved in anxiety should be achieved (Vervliet et al., 2013). If the related inhibitory fronto-limbic connectivity is already present prior to treatment, this may facilitate inhibitory learning to act. Furthermore, our results on inhibitory PFC-hippocampus connectivity point to reduced fear-memory retrieval (Heller & Bagot, 2020), which further facilitates the formation of the new fear-inhibitory memory trace and its competition with the fear excitatory CS-US association.

This model receives additional support by our findings on moderators of the within session extinction process itself. Those patients, who exhibited enhanced connectivity between regions related to the assessment of the need for emotion regulation (VLPFC; Kohn et al., 2014)

and the selection and implementation of adequate regulative strategies (VMPFC; Sheppes et al., 2015) also achieved more anxiety reduction within the exposure session. Furthermore, the VMPFC is thought to account for automatic emotion regulation, whereas the DLPFC and VMPFC have been related to voluntary emotion regulation (Golkar et al., 2012; Phillips et al., 2008). Heightened connectivity between those regions might therefore reflect enhanced balancing of those processes (Delgado et al., 2008; Zilverstand, Parvaz, et al., 2017). Consequently, fronto-limbic inhibition might be even stronger, if it is accompanied by enhanced intrinsic prefrontal connectivity within regions related to the different steps of (voluntary) emotion regulation (Sheppes et al., 2015).

To summarize, heightened visual processing constitutes a pathophysiological feature of anxiety disorders and is even pronounced if comorbid anxiety disorders are present. However, together with enhanced inhibitory fronto-limbic connectivity it might facilitate the formation of the new fear-inhibitory memory trace, which is the goal of fear extinction during exposure. Enhanced intrinsic prefrontal connectivity may further support this process as it may reflect enhanced emotion regulation capabilities. Deduced from this hypothetical working model, the support of those three moderating systems via additional or modified treatments is necessary to enhance exposure outcome also in those patients who would remain as non-responders when treated as usual.

5.3 The health economic impact of anxiety disorders

Providing adapted or add-on treatments for non-responding anxiety disorder patients, would not only aid in diminishing individual suffering. Due to the high prevalence of anxiety disorders (Wittchen et al., 2011), it would also substantially reduce their health economic impact. During a year, mental health conditions are estimated to affect about one quarter of the population worldwide (Holmes, Craske, & Graybiel, 2014). Across all known diseases, they constitute the leading cause of years lived with disability (Whiteford et al., 2013). Among mental health conditions, anxiety disorders constitute the most frequent category, with a 12-month prevalence of 14% (Wittchen et al., 2011). With a worldwide population of roughly 7.7 billion people (UN, 2019), this results in over one billion individuals affected by anxiety disorders across the globe. This high number of patients is related to an immense burden and suffering, which is reflected in anxiety disorders accounting for 14.6% of lost years of healthy life (disability-adjusted life years; DALY) caused by mental disorders (Murray et al., 2012; Whiteford

et al., 2013). However, anxiety disorders are not only accompanied by a high individual psychological burden. Due to the high number of affected individuals, they also substantially impact on the financial resources of public health care systems (Gustavsson et al., 2011). With respect to Europe, health care expenses due to anxiety disorders were estimated in 2010 with 74 billion euros (Gustavsson et al., 2011). Furthermore, they cause high indirect socioeconomic cost as they often interfere with work ability (Gustavsson et al., 2011; Lund et al., 2010; Wittchen et al., 2011). This indirect cost is estimated to even exceed direct expenses for the treatment of anxiety disorders (Gustavsson et al., 2011).

Besides pharmacotherapy, psychological treatments like CBT show strong evidence for addressing mental health conditions and especially anxiety disorders (Carpenter et al., 2018; Holmes et al., 2014; Holmes et al., 2018). However, 30-50% of anxiety disorder patients do not respond in a clinically significant manner thus leaving them with full or residual symptomatology and the related burden (Loerinc et al., 2015; Taylor et al., 2012). If all patients were treated, this would result in 500-700 million patients worldwide potentially achieving successful amelioration of symptoms by means of exposure-based CBT. Nevertheless, another 300-500 million people would be left with further suffering and disability. Holmes et al. (2014) recommend three steps to be taken to overcome the existing treatment response gap and to further improve the efficacy of psychological treatments: first, uncovering the mechanisms of existing treatments, second, optimizing them and developing further treatments, as well as third, establishing a stronger link between laboratory researchers and clinical practitioners. With respect to those steps, Holmes et al. (2014) further suggest the combination of neuroscientific and clinical research. The resulting discipline of mental health science should include the whole spectrum from basic animal models to clinical studies in humans (Holmes et al., 2014; Milton & Holmes, 2018).

The present thesis considers itself as a contribution to the process of bridging the gap between neuroscientific research on the underlying mechanisms involved in extinction and exposure treatment as well as their application within clinical practice. We investigated factors moderating the mechanism of action of exposure treatment with the goal of optimizing treatment, aiding in the development of further or supplemental treatments as well as providing starting points for clinical translation. In line with those ideas, the present work might in the long run support the reduction of suffering of the individual patient as well as the decrease of the health economic burden associated with anxiety disorders (Richter, Pittig, Hollandt, & Lueken, 2017).

5.4 Personalized treatments in psychiatry and novel methodological approaches

As mentioned within the previous paragraphs, neuroscience can substantially aid in improving psychotherapeutic treatments for mental disorders (Holmes et al., 2014). It is concerned with studying the brain and thus the organ that is primarily affected by mental conditions like anxiety disorders. Yet, neuroscientific research has related the symptoms of various mental disorders to neural alterations (see e.g. Balodis & Potenza, 2019; Matsubara et al., 2016; Molent, Olivo, Wolf, Balestrieri, & Sambataro, 2019; Shin & Liberzon, 2010). In turn, neuroscience has demonstrated psychotherapy to alter the brain as well (see e.g. Boccia, Piccardi, & Guariglia, 2016; Messina et al., 2013; Schmitt, Winter, Niedtfeld, Herpertz, & Schmahl, 2016). The more precise those treatment-induced neural changes target the neural pathophysiology of a certain mental disorder, the more effective the treatment will likely be (Lueken & Hahn, 2016). Unfortunately, neural alterations due to the same mental disorder are never fully identical across individuals. The same is true for the effect of psychotherapy on the brain. Even if a fully identical treatment would be applied, outcome is likely to vary between patients. Both phenomena are due to factors moderating the impact of a specific disorder on the brain as well as the impact of a certain treatment on the pathophysiological alterations, respectively (Ozomaro, Wahlestedt, & Nemeroff, 2013). Therefore, it is highly relevant to characterize patient and treatment attributes as precise as possible. This might enable the adaptation of treatments to the individual patient's needs. The related process is called personalization (Ozomaro et al., 2013).

Personalization is the maximal manifestation of stratification, which refers to the division of patients into groups according to their characteristics and likelihood of responding to a certain treatment (Ozomaro et al., 2013). This already enables a more precise selection of treatment options even though full personalization has not yet been achieved (Schork, 2015). Within the last years, personalization and stratification became a major focus of medical research even beyond mental disorders (Schork, 2015). This development is supported by new methodological advances, which allow for the facilitated grouping of patients according to multimodal characteristics (Bzdok & Meyer-Lindenberg, 2018; Etkin, 2014; Ozomaro et al., 2013). Such a novel approach is the use of algorithms (Shatte, Hutchinson, & Teague, 2019). They allow for achieving stratification with continuously increasing accuracy (Lueken & Hahn, 2020). Today,

those algorithms are already able to identify highly complex patterns that far outreach the associative performance of our brain. Those patterns can then be used for stratification. As the algorithm gathers its "knowledge" via a training phase on the available data, this process is referred to as machine-learning (Bishop, 2006). Especially within psychiatric and psychotherapeutic research, machine-learning algorithms are of high interest as the available data are of high complexity and dimensionality (e.g. behavioral observations, (epi)genetics, (f)MRI, self-assessments; Bzdok & Meyer-Lindenberg, 2018; Huys, Maia, & Frank, 2016; Lueken & Hahn, 2020). Nevertheless, machine-learning is not a panacea that is going to "cure" any problem clinicians face during treatment just in passing. To fully realize its potential, the algorithms have to be provided with data that previously have been related to the criterion according to which patients should be stratified (Beam & Kohane, 2018). When aiming at improving treatments, this criterion usually is treatment response or outcome. Hence, there is a high need for research covering the identification of moderators of treatment outcome. Machine learning subsequently provides the opportunity to combine multiple moderators to enhance accuracy of stratification and treatment outcome prediction (Bzdok & Meyer-Lindenberg, 2018; Lueken & Hahn, 2020; Niles et al., 2017). To achieve valid predictions for clinical practice, training data furthermore need to be representative for naturalistic clinical samples as otherwise accuracy of stratification and outcome prediction will be diminished (Sundermann et al., 2017).

However, stratification is only the first step on the way to improve response rates. Subsequently, the identification of suitable treatments for the different patient groups is essential. Known modifications for exposure treatment are e.g. deepened extinction, the increase of variability during exposure, the introduction of retrieval cues or the use of cognitive enhancers like d-cycloserine (Craske et al., 2018; Ebrahimi et al., 2020; Weisman & Rodebaugh, 2018). Nevertheless, all those strategies do not specifically focus on the neural substrates (e.g. connectivity) that characterize the respective patient groups. According to our findings, future studies should search for options that enable the modification of the three identified neural systems, which have been shown to moderate treatment outcome.

With respect to ventral visual pathway regions and their connectivity with the amygdala, a simple treatment modification might be the explicit and continuous focusing of gaze on the CS during exposure. Possibly, a reduction of visual distraction needs to be emphasized in patients characterized by low pre-treatment amygdala-visual connectivity. Pharmacologically, glucocorticoid administration has been shown to directly dampen amygdala-fusiform connectivity, which leads to reduced amygdala activation in response to phobic stimuli (Nakataki et

al., 2017). According to our results, the opposite effect would be beneficial for inhibitory learning to occur. Thus, antiglucocorticoids like mifepristone, ketoconazole or metyrapone (Gallagher et al., 2008) might be candidate substances, which possibly support visuo-limbic connectivity. Yet, they have been already shown to exhibit an antidepressant effect (Gallagher et al., 2008). As ventral visual pathway regions did only show up in the acquisition phase within the comorbidity study, we believe their activation as well as changes from pre- to posttreatment to be linked to extinction training rather than extinction recall. This would implicate add-on strategies for the support of visuo-limbic connectivity to be especially relevant immediately during exposure.

With respect to intrinsic PFC connectivity in relation to emotion regulation capabilities as well as fronto-limbic inhibition, strategies like neurofeedback, tDCS, TMS or emotion regulation trainings might constitute promising treatment modifications (Dittert et al., 2018; Herrmann, 2019; Lorenzetti et al., 2018; Neacsiu et al., 2014). Overall, findings on visuo-limbic as well as fronto-limbic and intrinsic prefrontal connectivity from our resting-state analysis are likely to be interdependent (see working model and Figure 8). As enhanced fronto-limbic connectivity suggests pronounced emotion regulation capacities, those patients might also exhibit less (attentional) avoidance behavior, which may lead to enhanced visuo-limbic connectivity compared to non-responders. This is in line with findings on the lack of executive control being the major cause of attentional bias in anxiety disorders (McNally, 2019). Whether augmentation strategies that may improve fronto-limbic connectivity might also enhance visuo-limbic connectivity needs to be investigated.

5.5 Limitations

Even though our findings on moderators of treatment outcome overlap to a certain extent across the three investigated mental conditions, our findings are limited by the disorders, which were studied. As fear extinction is thought to be a transdiagnostic mechanism, we would hypothesize the three identified systems to be relevant transdiagnostically as well. However, this needs to be investigated within future studies. Upcoming studies should also assess other combinations of comorbid disorders within as well as beyond the spectrum of anxiety disorders. Possibly, disorders that interfere with visual processing and visuo-limbic connectivity, fronto-limbic, or intrinsic PFC connectivity like eating disorders (Friederich, Wu, Simon, & Herzog, 2013), borderline personality disorder (Wolf et al., 2011; Xu et al., 2016), or bipolar disorder

(Vargas, López-Jaramillo, & Vieta, 2013) might lead to detrimental outcome. Due to the choice of functional connectivity, directionality of connectivity remains unclear. Besides directionality, our studies do not allow for differentiating between moderators of extinction training and moderators of extinction recall. This is essential with respect to the choice of potential treatment modifications and the timepoint when they should be applied. Related to this limitation, both studies lack the investigation of long-term effects and thus also moderators of long-term extinction recall. This could have been achieved via the use of follow-up outcome data. It is further unknown, whether the three mentioned systems moderated only fear extinction and inhibitory learning or also other mechanisms of action like self-efficacy or placebo which contribute to treatment outcome. Neurofunctionally-based patient stratification has been repeatedly demonstrated to allow a high prediction accuracy with respect to treatment outcome (Doehrmann et al., 2013; Lueken et al., 2016; Whitfield-Gabrieli et al., 2016). However, fully personalized treatments will only be achieved if therapist variables will be integrated as well and interactions of patient and therapist characteristics are investigated (e.g. neural patient characteristics x therapist personality). This would also be in line with the idea of mental health science as proposed by Holmes et al. (2014). Both studies presented here, did not include such data as it was the goal to specifically study neural patient characteristics. However, especially the way how therapists achieve motivation to overcome avoidance behavior and the interaction of those strategies with the underlying neural patient characteristics might be promising with respect to the prediction of treatment outcome.

6 Conclusion and future directions

Within this thesis, we were able to extend scientific knowledge on moderators of treatment outcome in anxiety disorders and highlight the relevance of mental health science to bridge the gap between basic research and clinical practice. Overall, our results point to treatment responders exhibiting a prepared brain in terms of beneficial preconditions for successful inhibitory learning during exposure. Future studies should try to further characterize the neural signatures moderating treatment outcome in anxiety disorders and test their interrelations as hypothesized by our working model. Those characteristics might subsequently be used for the development of machine-learning algorithms, which predict the likelihood of good or poor treatment outcome prior to exposure. The algorithms should incorporate information on the neural constitution of the patient, including comorbidity and connectivity to enhance predictive accuracy. Like a soil sample, the machine-learning algorithm would enable the evaluation of the fruitfulness of the soil where the seed of inhibitory learning will be sown. If the algorithm predicts impaired or even poor treatment outcome due to unfavorable neural signatures, it may suggest a specific treatment modification or enrichment, which can serve as fertilizer of the patient's neural soil. Research on fear conditioning and extinction as well as our results favor a transdiagnostic approach for the diagnosis and treatment of anxiety disorders as it is intended by the RDoC initiative (Frank, Jacobson, Hurley, & McKay, 2017; Insel et al., 2010; Lang, McTeague, & Bradley, 2016). Therefore, the selection of the adequate treatment modification or augmentation strategy should not be dependent on diagnostic categories as well. Instead, it should rely on the neurobiologically informed identification of dysfunctions within overarching functional domains (Fernandez, Jazaieri, & Gross, 2016). In the long run, research on personalized treatments needs to overcome a solely patient-centered view and include therapist-variables and their interaction with patient characteristics like resting-state functional connectivity as well. In line with the idea of mental health science, as proposed by Holmes et al. (2014), this would support a comprehensive understanding of the whole therapeutic process. Together with the application of new methodological advances like machine learning and artificial intelligence, this might enable clinicians to provide individually tailored options to successfully exploit the strengths of exposure treatment in all anxiety disorder patients.

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Index of Abbreviations

In order of appearance:

CBT	Cognitive Behavioral Therapy
PD	Panic Disorder
AG	Agoraphobia
SAD	Social Anxiety Disorder
KVT	Kognitive Verhaltenstherapie
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., text revision
PD/AG	Panic Disorder with/without Agoraphobia
SCID	Structured Clinical Interview for DSM
ACC	Anterior cingulate cortex
PFC	Prefrontal cortex
PAG	Periaqueductal grey
MRI	Magnetic Resonance Imaging
fMRI	Functional Magnetic Resonance Imaging
rsFC	Resting-state functional connectivity
MPFC	Medial prefrontal cortex
CS	Conditioned stimulus
US	Unconditioned stimulus
UR	Unconditioned response
CR	Conditioned response
BNST	Bed nucleus of the stria terminalis
VMPFC	Ventromedial prefrontal cortex
PCC	Posterior cingulate cortex
DLPFC	Dorsolateral prefrontal cortex
CS+	Conditioned stimulus associated with the unconditioned stimulus
CS-	Conditioned stimulus not associated with the unconditioned stimulus
R	Response
O	Outcome
GAD	Generalized Anxiety Disorder
AN	Affective network
SN	Salience network
ECN	Executive control network
FPN	Fronto-parietal network
DMN	Default mode network
VAN	Ventral attention network
VLPFC	Ventrolateral prefrontal cortex
MTG	Middle temporal gyrus
VR	Virtual reality
3-D	Three-dimensional

VRET	Virtual reality exposure treatment
RoF	Return of fear
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
5-HTTLPR	5-Hydroxytryptamine-transporter-linked polymorphic region
MAO-A	Monoamine oxidase A
IFG	Inferior frontal gyrus
SFG	Superior frontal gyrus
CIDI	Composite International Diagnostic Interview
SIGH-A	Structured Interview Guide for the Hamilton Anxiety Rating Scale
CGI	Clinical Global Impression
BSI	Brief Symptom Inventory
SIAS	Social Interaction Anxiety Scale
SPS	Social Phobia Scale
ITI	Inter-trial interval
SAM	Self-assessment manikin
LCD	Liquid-crystal display
3-T	Three tesla
mm	Millimeters
ms	Milliseconds
TE	Echo time
TR	Repetition time
SPM	Statistical Parametric Mapping
BOLD	Blood-oxygen-level-dependent contrast
MNI	Montreal Neurological Institute
FWHM	Full width at half maximum
ASI	Anxiety Sensitivity Index 3
BDI	Beck Depression Inventory II
ANOVA	Analysis of Variance
BSI-Sens	Brief Symptom Inventory, interpersonal sensitivity subscale
STP	Superior temporal pole
IFO	Inferior frontal operculum
RDoC	Research Domain Criteria
BAT	Behavioral Avoidance Test
WS-ext	Within-session extinction
CONSORT	Consolidating Standards of Reporting Trials
SPQ	Spider Phobia Questionnaire
MPRAGE	Magnetization-prepared rapid gradient echo
FOV	Field of view
EPI	Echo-planar imaging
ROI	Region of interest
AAL	Automated Anatomical Labeling Atlas
CSF	Cerebrospinal fluid
GLM	General linear model
ICA	Independent component analysis
FDR	False discovery rate

MFG	Middle frontal gyrus
SPG	Superior parietal gyrus
TMS	Transcranial magnetic stimulation
rTMS	Repetitive transcranial magnetic stimulation
tDCS	Transcranial direct-current stimulation

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Appendix

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Appendix A – Reprint permission for Seeger et al. 2019

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Appendix B – Overview of assessments of the SpiderVR study

Modified from Schwarzmeier et al. (2019):

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**
Fragebogen Ekel und Angst vor Spinnen (FEAS)[1]	**X**			**X**	**X**
State-Trait Anxiety Inventory (STAI-Trait)	**X**			**X**	**X**
Beck Depression Inventory II (BDI-II)	**X**			**X**	**X**
BEHAVIORAL					
BAT	**X**			**X**	**X**
NEUROBIOLOGICAL					
blood sampling	**X**			**X**	**X**
EDA	**X**			**X**	**X**
(f)MRI		**X**			
ADDITIONAL PSYCHOLOGICAL CHARACTERISTICS					
Igroup Presence Questionnaire (IPQ)			**X**		
Anxiety Sensitivity Index (ASI)	**X**			**X**	**X**
General Self-Efficacy Scale (GSE)	**X**			**X**	**X**
PROMIS Scales for DSM-5 (anxiety)	**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)[2]	**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)[3]	**X**				
Brief COPE	**X**				
Fragebogen zur Angst vor Spinnen (FAS)[4]	**X**				
Behavioral Inhibition System – Beahvioral 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] "Questionnaire on Disgust and Fear of Spiders"
[2] German version of the Center for Epidemiological Studies Depression Scale (CES-D-scale, NIMH)
[3] "Brief questionnaire about stresses and strains"
[4] German version of Fear of Spiders Questionnaire (FSQ, Szymanski & O'Donohue, 1995)
[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"

IPQ (Schubert, Friedmann, & Regenbrecht, 2001), ASI (Alpers & Pauli, 2001), BDI-II (Hautzinger et al., 2006), GSE (Schwarzer & Jerusalem, 1999), PROMIS (Wahl, Löwe, & Rose, 2011), STAI (Laux, 1981), UI-18 (Gerlach, Andor, & Patzelt, 2008), BAI (Margraf & Ehlers, 2007), LTE (Terry S Brugha & Cragg, 1990), LSAS (Stangier & Heidenreich, 2004), ADS (Hautzinger, Bailer, Hofmeister, & Keller, 2012), ACQ (Ehlers, Margraf, & Chambless, 2001), PSWQ (Stöber, 1998), SPAI (Fydrich, 2002), PANAS (Krohne, Egloff, Kohlmann, & Tausch, 1996), 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, & Brocke, 2001), TICS (Schulz, Schlotz, & Becker, 2004), SVF-78 (Janke, 2002), CERQ (Loch, Hiller, & Witthöft, 2011), SDS-CM (Luck & Timaeus, 1969), TEMPS-A (Akiskal, Brieger, Mundt, Angst, & Marneros, 2002), SS-A (Laireiter, 1996), BSSS (Schwarzer & Schulz, 2003).

List of publications

Seeger, F., Yang, Y., Straube, B., Kircher, T., Höfler, M., Wittchen, H.-U., . . . Lueken, U. (2019). Clinical and Neurofunctional Substrates of Cognitive Behavioral Therapy on Secondary Social Anxiety Disorder in Primary Panic Disorder: A Longitudinal fMRI Study. *Psychotherapy and psychosomatics, 88*(1), 48-51.

Schwarzmeier, H., Leehr, E. J., Böhnlein, J., **Seeger, F. R.**, Roesmann, K., Gathmann, B., . . . Dannlowski, U. (2019). 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, n/a*(n/a), e1812. doi:10.1002/mpr.1812

Affidavit

I hereby confirm that my thesis entitled “Moderators of exposure-based treatment outcome in anxiety disorders: an fMRI approach” 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.

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