Panic disorder with agoraphobia from a behavioral neuroscience perspective: Applying the research principles formulated by the Research Domain Criteria (RDoC) initiative

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Abstract

In the current review, we reconceptualize a categorical diagnosis—panic disorder and agoraphobia—in terms of two constructs within the domain “negative valence systems” suggested by the Research Domain Criteria initiative. Panic attacks are considered as abrupt and intense fear responses to acute threat arising from inside the body, while anxious apprehension refers to anxiety responses to potential harm and more distant or uncertain threat. Taking a dimensional view, panic disorder with agoraphobia is defined with the threat-imminence model stating that defensive responses are dynamically organized along the dimension of the proximity of the threat. We tested this model within a large group of patients with panic disorder and agoraphobia (N = 369 and N = 124 in a replication sample) and found evidence that panic attacks are indeed instances of circa strike defense. This component of the defensive reactivity was related to genetic modulators within the serotonergic system. In contrast, anxious apprehension—characterized by attentive freezing during postencounter defense—was related to general distress and depressive mood, as well as to genetic modulations within the hypothalamic-pituitary-adrenal (HPA) axis. Patients with a strong behavioral tendency for active and passive avoidance responded better to exposure treatment if the therapist guides the patient through the exposure exercises.

Descriptors: Anxiety, Startle Blink, Genetics, Psychopathological, Psychopathology, Autonomic

First clinical trial

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Introduction

The National Institute of Mental Health (NIMH) has recently introduced its Research Domain Criteria (RDoC) program with the aim to “develop for research purposes new ways of classifying mental disorders based upon dimensions of observable behavior and neurobiological measures” (Cuthbert & Insel, 2013; Kozak & Cuthbert, 2016). Similar calls for action have been recently proposed within the European Roadmap for Mental Health Research (ROAMER; Schumann et al., 2014; Wittchen et al., 2014), emphasizing the need for developing synergistic approaches for linking traditional and novel diagnostic approaches. In the present article, we first describe the diagnostic criteria for panic disorder and agoraphobia as currently used in the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5; APA, 2013), and then redefine these diagnostic features in terms of the research domains and constructs proposed in the RDoC framework. By applying the defense cascade model derived from animal research in behavioral neuroscience, we then describe defensive behaviors in a large group of patients with the principal diagnosis of panic disorder with agoraphobia assessed during a standardized behavioral avoidance test. We then link these defensive behaviors to physiological measures of defensive reactivity as well as to dimensional trait-like fear measures and genetic markers using multiple units of analysis. Finally, based on the data obtained from a multicenter randomized clinical trial (Gloster et al., 2011, 2013) investigating the mechanisms of action of cognitive behavior therapy for panic disorder with agoraphobia, we test whether defensive reactivity is related to clinical outcome and whether it can predict differential effects.

Diagnostic Criteria Defining Panic Disorder and Agoraphobia

According to DSM-5 (APA, 2013) recurrent (more than one) unexpected panic attacks (Criterion A) are one essential diagnostic feature of panic disorder. A panic attack is defined by “an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes” (crescendo criterion) “and during which time four (or more) of a list of 13 physical and cognitive symptoms have occurred,” as reported by the patient. The term unexpected means that the individual does not perceive any obvious cue or trigger at the time the panic attack occurs. The judgment, whether the panic attack is unexpected or not, is made by the clinician.

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The RTC project was approved by the Ethics Committee of the Medical Faculty of the Technical University of Dresden (EK 164082006). The neuroimaging components were approved by the Ethics Committee of the Medical Faculty of the Rheinisch-WestfälischeHochschule University Aachen (EK 073/07). The experimental pharmacology study was approved by the Ethics Committee of the state of Berlin (EduaCT: 2006-00-4860-29).

The study was registered with the ISRCTN: ISRCTN80046034.

Second clinical trial

Funding/Support: This work is part of the German multicenter trial: Mechanisms of CBT-treatment effects in patients with panic disorder and panic disorder with agoraphobia: The role of interoceptive fear and exposure augmentation (MCBT-PDAS). The study is funded by the German Federal Ministry of Education and Research (BMBF, 01GV0614) as part of the larger BMBF Psychotherapy Research Initiative Improving the Treatment of Panic Disorder.

Centers of the Multicenter Trial: Principal investigators (PIs) with respective areas of concentration of the MCBT-PDAS are Alfonso Ham (Greifswald: PI Psychophysiology); Thomas Lang (Bremen: Study Director for the Randomized Clinical Trial [RCT] and Manual Development); Alexander L. Gerlach (Münster: PI Panic subtypes); Georg W. Alpers (Mannheim: PI Ambulatory assessment); Christiane Pané-Farré (Greifswald: PI Psychoophysiology and Panic Disorder); Tilo Kircher (Marburg: PI for functional neuroimaging); and Jürgen Deckert (Würzburg: PI for Genetics). Additional site directors in the RCT component of the program are Winfried Rief (Marburg) and Paul Pauli (Würzburg).

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In addition to such recurrent unexpected panic attacks, the individual has to acknowledge the experience of “persistent (for one month or more) concern or worry about additional panic attacks and their consequences” (Criterion B1), which could be physical concerns, such as the worry that panic attacks reflect the presence of life-threatening illnesses (e.g., cardiac disease, seizure disorder), social concerns (fear of being judged negatively by others because of visible panic symptoms), and concerns about mental functioning (“going crazy”) or individuals have to show a significant maladaptive change in behavior related to the attacks (Criterion B2). “Examples of such changes in behavior include avoiding physical exertion, reorganizing daily life to ensure that help is available in the event of a panic attack, restricting usual daily activities and avoiding agoraphobia-type situations, such as leaving home, using public transportation, or shopping” (APA, 2013).

The association between panic disorder and agoraphobic avoidance has been the focus of a long-standing controversy. Beginning with the DSM-III-R (APA, 1987), agoraphobia was considered to be a consequence or complication of a panic disorder and could not be coded as unique disorder in the DSM-IV-TR (APA, 2000). Epidemiological evidence, however, suggests that agoraphobia—although being frequently associated with panic disorder (in approximately 50% of all cases)—can exist independently, that is, without any history of panic disorder or even panic-like symptoms (Pané-Farré et al. 2014; Wittchen, Gloster, Beesdo-Baum, Fava, & Craske, 2011). Moreover, agoraphobia just as frequently precedes reports of panic attacks as panic attacks precede agoraphobia (Pané-Farré et al. 2013). As a consequence, agoraphobia and panic disorder are now codable as separate disorders in DSM-5 (APA, 2015). Here, agoraphobia is defined as marked fear or anxiety about two (or more) of five clusters of situations (Criterion A). These include situations that are either characterized by entrapment (public transportation, enclosed places, standing in line, or being in a crowd) or situations in which in case of emergencies no immediate help is available such as being in open spaces or outside of the home alone. As in the case of specific phobias, these clusters of situations are avoided when possible (Criterion B). In the current article, we will address some of these diagnostic controversies taking into account the research domains and constructs proposed by the RDoC.

Defining Panic Disorder With Agoraphobia in Terms of the Negative Valence Systems Domain

The phenomenology of panic disorder and agoraphobia can best be conceptualized within the domain negative valence systems comprising five different constructs. A panic attack is a prototypical example of an abrupt and intense fear response to an acute threat. Threat stimuli are species specific and can comprise external stimuli such as other animals (e.g., predators), nociceptive events (e.g., painful stimuli), or harmful conspecifics (e.g., rivals). Note that acute threat can also arise from inside the body. For example, hypoxia or hypercapnia result in the perception of acute air hunger or dyspnea, one of the central symptoms panic attacks (see Preter & Klein, 2008; Schimitel et al., 2012). Moreover, other interoceptive signals like visceral pain (e.g., ischemia of the heart which is perceived as acute chest pain overlying the sternum) are potent acute internal threat stimuli that can cause panic attacks.

In contrast to panic attacks as prototypical expressions of fear responses to acute internal threat stimuli, concerns and worries about the potential harm or consequences of these panic attacks (Criterion B1 of panic disorder) can be conceptualized as responses to potential threats (anxiety) within the negative valence system.

Figure 1. A: The Threat Imminence Model suggesting that defensive reactivity is organized as a cascade of three different stages depending on the distance (proximity) of the threat. B: Application of the Threat Imminence Model to describe the psychopathology of panic disorder.

Anxiety about potential harm is more ambiguous, activated by physically or psychologically more distant or uncertain threat. In patients with panic disorder, such anxious apprehension involves increased vigilance to cues from the body and enhanced risk assessment, and is qualitatively distinct from responses to acute threat. Animal data suggest that these different defensive behaviors might be dynamically organized along a dimension switching from one to the other depending upon the perceived proximity or imminence of the threat, as outlined in the threat imminence model by Fanselow (1994; see also Blanchard, 1997; Lang, Bradley, & Cuthbert, 1997). If an organism is in a context where threat has been encountered previously but has not yet been detected (pre-encounter defense), preemptive behavior is engaged including threat-nonspecific vigilance. As soon as a threat is detected (postencounter defense), attention is selectively allocated to the threat cue and defensive response output is characterized by fear bradycardia (Campbell, Wood, & McBride, 1997), potentiation of the startle reflex gated through the central nucleus of the amygdala (Lang, Davis, & Öhman, 2000), and motor “freezing,” depending on projections from amygdala to the ventral periaqueductal gray (vPAG) in the midbrain (Fanselow, 1994; Maren, 2001; Morgan & Carrive, 2001). Active defensive behavior (active avoidance, flight or fight) is initiated during circa strike defense, mediated by the dorsal periaqueductal gray (dPAG) that directs the expression of escape behavior (Kim et al., 2013, LeDoux, 2012) accompanied by a general discharge of the sympathetic nervous system (Cannon, 1932). The left panel of Figure 1 depicts a schematic chart of the threat imminence model.

As outlined above, panic attacks are abrupt surges of intense fear characterized by rapid increase in heart rate and skin conductance (Cohen, Barlow, & Blanchard, 1985; Meuret et al., 2012) often associated with overwhelming behavioral action tendencies for active avoidance/escape (Bouton, Mineka, & Barlow, 2001), suggesting that panic attacks might be instances of a circa strike defense state—an idea first proposed by Craske (1999) and elaborated by Bouton, Mineka, and Barlow (2001). Recent animal data also support this view. Infusion of low doses of potassium cyanide (KCN) produces hypoxia in the dPAG and facilitates active avoidance and escape behavior elicited by electrical stimulation of the dPAG. In contrast, lesions of the dPAG abolish KCN-evoked escape behavior (Schimitel et al., 2012). Hypoxia can be considered as an acute internal threat triggering a panic attack as circa strike defense (Canteras & Graeff, 2014). The second component
of panic disorder—anxious apprehension—can be conceptualized as postencounter defense within the threat-imminence model. Individuals with panic disorder perceive future panic attacks as uncontrollable and unpredictable and are extremely vigilant for somatic symptoms that might signal the beginning of a new panic attack. If such mild somatic symptoms are detected, attentive freezing is engaged.

There is evidence that the detection of mild body symptoms indeed leads to anticipatory anxiety and attentive freezing in patients with panic disorder. Melzig, Holtz, Michalowski, and Hamm (2011) used the startle probe methodology to study anxious apprehension during perception of mild body symptoms during early recovery from a guided hyperventilation task. Because immediately after the hyperventilation task the blood partial pressure of carbon dioxide (pCO₂) is still below 30 mmHg for approximately 2 minutes mild body symptoms are still present without interference from the guided hyperventilation procedure itself. Startle probes were presented during recovery from the hyperventilation task (20 cycles per minute; increased tidal volume until target pCO₂ level of 20 mmHg was reached) as well as after “recovery” from normoventilation (spontaneous breathing). As predicted, patients with panic disorder showed a clear potentiation of their startle responses during recovery from hyperventilation compared to the control condition (see Hamm, Richter, & Pané-Farré, 2014). Healthy controls did not show any startle potentiation after recovery from hyperventilation although they had a comparable course of pCO₂ during this phase (Melzig et al., 2011). These data suggest that the perception of mild body symptoms activates postencounter defense in these patients that parallels the defensive response pattern evoked by conditioned external stimuli in fear conditioning experiments both in animals (see Davis & Whalen, 2001) and humans (Hamm & Weike, 2005).

Pre-encounter defense is activated when the individual enters the context in which a previous panic attack has been experienced but body symptoms have not been detected yet. During this stage, preemptive behavior is engaged including safety behavior but also threat-nonspecific hypervigilance. Increased sensitization of the attention system—as indexed by greater P1/N1 amplitudes of the event-related potentials to fear-relevant but also neutral stimuli—was found when individuals with specific phobia were in a context where visual phobic stimuli might occur (see Michalowski, Melzig, Stockburger, Schupp, & Hamm, 2009; Michalowski, Pané-Farré, Löw, & Hamm, 2015). Passive agoraphobic avoidance occurs very early in the defense cascade and in case of passive avoidance even prior to pre-encounter defense and is motivated by anxious apprehension of the expected potential threat (e.g., a panic attack) in a specific context. Supporting this view, Craske, Rapee, and Barlow (1988) demonstrated that perceived probability of panicking in a specific situation was the strongest predictor ($r = .49$) for active and passive avoidance of a variety of behavioral avoidance tests. These data are particularly important, because changing probability estimates of an aversive outcome are important ingredients of extinction learning. Violations of such expectations would induce a prediction error (Rescorla & Wagner, 1972) initiating extinction learning, which is considered to be one of the central mechanisms of exposure therapy.

Empirical Evaluation: Defensive Behaviors in Patients With Panic Disorder and Agoraphobia

We tested defensive reactivity using multiple units of analysis in a subgroup of 345 (259 female patients) patients from a total sample of 369 patients all of whom were diagnosed with a principal diagnosis of panic disorder with agoraphobia (PD/AG) and enrolled for a multicenter randomized controlled clinical trial study, Mechanisms of Action in Cognitive Behavioral Therapy (MAC; Gloster et al., 2009). Patient recruitment, inclusion and exclusion criteria of the multicenter RCT study, diagnostic tools and procedures, as well as patients’ sociodemographic characteristics are described elsewhere (Gloster et al., 2009, 2011).

Guided by the observation emphasized in the RDoC initiative that individuals with different characteristics can fall into the same diagnostic category, the current article focuses on different patterns of defensive reactivity of this large patient group assessed in a standardized behavioral avoidance task that was part of the diagnostic procedure prior to therapy. We measured self-reported anxiety, defensive behavior, protective reflex modulation, and autonomic responses during anticipation of (patients were sitting in front of the test chamber with its door open for 10 minutes) and exposure to a small (75 cm wide, 120 cm long, and 190 cm high) dark and closed test chamber (for a maximum of 10 minutes), constructed according to descriptions by Öst, Johansson, and Jerrenmalm (1982). Rachman and colleagues (Rachman, Levitt, & Lopatka, 1988; Rachman & Taylor, 1993) have successfully used this test as an experimental model to investigate physiological and cognitive symptoms of panic attacks in patients with claustrophobia. Because marked fear of entrapment and avoidance of being in enclosed places is also a prominent symptom in patients with panic disorder and agoraphobia (Arrindell, Cox, Van der Ende, & Kwee, 1995; Cox, Swinson, Kuch, & Reichman, 1993; Kwon, Evans, & Oei, 1990; Rodriguez, Pagano, & Keller, 2007), we expected to evoke defensive responses during this test in a large proportion of the PD/AG patient group.

During exposure to the behavioral avoidance test (BAT), patients were sitting in the chamber with the door locked from the outside by the experimenter. Patients were instructed to remain in the chamber for as long as possible and to knock on the wooden door if they wanted to end the exposure before the maximum exposure time elapsed (which was unknown to the patients). They were instructed to press a button whenever they experienced a panic attack in the chamber. The output of the button press was digitized and recorded as a separate channel in order to synchronize the onset of self-reported panic attacks with physiological recordings.

Applying this standardized behavioral avoidance test, we found that 236 patients (68.4%) reported medium to high levels of anxiety associated with physiological and behavioral indices of increased defensive response engagement (Richter et al., 2012). These data suggest that two thirds of all PD/AG patients show symptoms of fear when enclosed in this situation. Defensive reactivity, however, differed substantially among patients, although the same principal diagnosis based on the categorical classification of indicative symptom reports was assigned to all patients. Thirty-nine patients (11.3%) refused to enter the chamber after the anticipation period (“active avoiders/escapers”); 72 patients (20.9%) entered the test chamber after the anticipation period but terminated exposure prematurely (“active avoiders/escapers”; duration of exposure varied between 3 and 580 seconds, $M = 225.6; SD = 171.0$). One hundred twenty-five patients (36.2%) remained in the chamber despite medium to high levels of reported anxiety (“anxious completers”). These patients also showed a significant potentiation of the startle response, and physiological indices of fears, that is, significantly elevated heart rate and skin conductance levels during the entire duration of exposure (10 min) relative to the patients with panic disorder with agoraphobia ($N = 109; 31.6%$) who did not report
Table 1. Mean Scores (and Standard Deviations) of the Reported Intensity of Agoraphobic Avoidance During All-Day Life Assessed With the Mobility Inventory (MI; Subscale: Alone; Range 1-5) for Patients With Panic Disorder With Agoraphobia (PD/AG) who Showed Active/Passive Avoidance During the BAT Compared to Those PD/AG Patients who Completed the Test Without Showing Any Passive or Active Avoidance Behavior. Situations Listed in the MI Were Clustered Into the Five Categories Listed in the Diagnostic Criteria for Agoraphobia in the DSM-5 With MI Items in Brackets. Statistical Results of the Between-Group Comparisons (t test) Are Presented in the Last Column

<table>
<thead>
<tr>
<th>Clusters of situations</th>
<th>PD/AG patients with active/passive avoidance during the BAT (N = 130)</th>
<th>PD/AG patients with no active/passive avoidance during the BAT (N = 304)</th>
<th>Results of the statistical between-group comparisons (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Using public transportation (cars [at any time and on expressways], buses, trains,</td>
<td>3.60 (1.09)</td>
<td>3.16 (1.05)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>subway, ships, planes)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Being in open spaces (open spaces [outside and inside], high places, bridges,</td>
<td>2.36 (0.93)</td>
<td>2.21 (0.91)</td>
<td>.11</td>
</tr>
<tr>
<td>walking on the street)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Being in enclosed spaces (theaters, supermarkets, shopping malls, classrooms,</td>
<td>3.09 (0.92)</td>
<td>2.69 (0.89)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>restaurants, museums, elevators, stadiums, garages, enclosed spaces, staying home</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alone)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Standing in line or being in a crowd (standing in lines, parties or social</td>
<td>3.27 (1.02)</td>
<td>3.05 (1.06)</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>gatherings, being in a crowd)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Being outside of the home alone (being far away from home)</td>
<td>3.69 (1.35)</td>
<td>3.16 (1.40)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>MI total score</td>
<td>3.11 (0.84)</td>
<td>2.78 (0.82)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

any anxiety during entrapment (“nonanxious completers”) (see Richter et al., 2012).

These differences in defensive reactivity during exposure to the same standardized BAT were replicated in a second sample of 154 patients enrolled for a second randomized multicenter treatment trial in the MAC study. Inclusion and exclusion criteria were identical to those employed in the first RCT, except that 30 patients were included with a principal diagnosis of panic disorder without agoraphobia. The remaining 124 patients were diagnosed with the principal diagnosis of panic disorder with agoraphobia. In the group of patients with PD/AG defensive reactivity in the standardized BAT was assessed 119 patients. As in the previous sample, two thirds of the patients (N = 77; 64.7% of the 119 PD/AG patients) showed clear evidence of defensive reactivity during exposure to this test as indexed by increased reported anxiety, potentiation of startle and increase in autonomic arousal, while 35.3% of the sample completed the test without significant symptoms of anxiety. Again, replicating the results of the first study, 8.4% (N = 10) of this patient group refused to enter the chamber (“passive avoiders”) and 16.8% (N = 20) terminated the task prematurely (active avoiders/escapers”). As expected, defensive behavior in the standardized BAT was related to reported agoraphobic avoidance as assessed with the Mobility Inventory (MI).

In Table 1 the situations were clustered according to the five categories of situations that are listed in the DSM-5. Patients showing passive and active avoidance in the standardized BAT also reported stronger avoidance in all clusters of agoraphobic situations except for being in open spaces. Avoidance tendencies of being in open spaces were overall rated as less severe compared to all other clusters of situations in our sample, suggesting that these situations are not as typical for agoraphobic avoidance as was originally thought (Westphal, 1871). Interestingly, patients showing behavioral avoidance in the BAT were more likely to also avoid situations like being far away from home or being in crowds. This suggests that observed avoidance behavior during the BAT might not only be restricted to enclosed situations but might rather reflect a more generalized disposition for avoidance that is also evident in other agoraphobic situations. Thus, avoidance behavior observed in this specific behavioral task might be used to examine associations to genetic risk markers of such avoidance disposition on a behavioral level.

Although all patients (N = 464) were diagnosed with PD/AG as the principal diagnosis, the majority of patients (82%) were diagnosed with additional comorbid disorders. The most frequent comorbid disorder was Specific phobia. Of all PD/AG patients, 65.5% were diagnosed with this additional disorder. Two hundred twenty-seven patients (48.9%) were diagnosed with a Specific Phobia—situational type comprising claustrophobic fears. Indeed, this group of patients did show significantly more active and passive avoidance behavior in the BAT. Moreover, these patients reported more fear and also showed stronger initial heart acceleration compared to PD/AG patients without this comorbid diagnosis, suggesting that claustrophobic fears moderate defensive responding during this task. However, number of comorbid diagnoses also influenced avoidance behavior observed in the BAT (number of comorbid diagnoses varied between patients from 1–2 [44%], over 3–4 [27%], up to 5+ [11%]). Patients with five or more comorbid diagnoses showed significantly more avoidance behavior than all other patients (p < .05). Moreover, number of comorbid diagnoses was also related to severity of agoraphobic avoidance as assessed by self-report (MI) or by the therapist (Clinical Global Impression; Agoraphobic Avoidance). Frequency of comorbid diagnoses was also associated with increased overall symptom severity (assessed with the Brief Symptom Inventory [BSI]) and reported depressive symptoms (assessed with the Beck Depression Inventory—II [BDI-II]) replicating previous findings (McTeague, Lang, Laplante, & Bradley, 2011).

Defensive Reactivity During Escape and Acute Panic

The analysis of defensive reactivity in patients who showed active avoidance revealed that heart rate and skin conductance increased linearly during the last 60 seconds just prior to escape from the chamber which was initiated at the peak of the autonomic surges (see upper panel of Figure 2). Interestingly, startle response
lus was also strongly attenuated when individuals had the option to actively avoid the aversive threat, reflecting focused preparation for effective escape with reduced attention allocated to the task-irrelevant probe stimulus.

This pattern of defensive reactivity observed during active avoidance and preparation for escape from an aversive electrical stimulus or from the BAT resembled the response pattern found during acute panic attacks experienced by PD/AG patients during exposure in the small, narrow chamber. Twenty-six patients (7.5% of the patients) reported 34 panic attacks during exposure by pressing the “panic button.” Startle blink magnitudes are presented in µVolts averaged across two probe stimuli presented prior to the button press and three probes presented after the button press. The lower panel of Figure 2 depicts startle magnitudes and heart rate changes averaged in 5-second bins starting 30 seconds prior to button press and 60 seconds during and after the button press for those 11 reported panic attacks for which both physiological measures were available (see Richter et al., 2012 for a more detailed analysis of these data). In line with findings from an ambulatory monitoring study (Meuret et al., 2011), heart rate increased prior to the button press, suggesting that increase in autonomic arousal indeed triggered the experience of the panic attack. As during preparation for active avoidance, startle magnitudes were also inhibited during acute panic attacks, suggesting that acute panic attacks might be instances of circa-strike defense possibly associated with the perception of acute threat signals from inside the body (e.g., dyspnea). Interestingly, there are early reports by Nashold, Wilson, and Slaughter (1974) that electrical stimulations of the periaqueductal gray evoked acute panic attacks in humans (see Schenberg et al., 2014 for review), supporting the view that panic attacks might be instances of circa-strike defense modulated by dlPAG.

**Relating Defensive Reactivity to Dimensional Risk Factors: Psychological Traits and Genetic Markers**

Using a standardized behavioral avoidance test, we found a large heterogeneity in defensive responding of patients, all diagnosed with the same principal diagnosis—PD/AG. We also found that defensive responses were dynamically organized depending upon the dominant action disposition that is activated during approaching threat. In the next step, we started to investigate whether we would find meaningful associations between individual patterns of defensive reactivity, dimensional trait like risk factors and genetic dispositions (Domschke et al., 2011; Hohoff et al., 2015; Reif et al., 2014; Straube et al., 2014).

Stimulated by cognitive models of panic disorder (Beck & Emery, 1985) Reiss (1991) and McNally (1994) suggested that individuals can be characterized by a trait like cognitive predisposition—labeled anxiety sensitivity (AS)—to misinterpret ambiguous cues and somatic symptoms as being predictive for deleterious physical, psychological, and social consequences. AS is defined as a set of trait-like beliefs that the fear- or anxiety-related somatic sensations indicate danger-associated harmful consequences. As measured with the Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986), high AS is considered to be predictive for the occurrence of panic attacks and the development of PD (Schmidt, Zvolensky, & Maner, 2006; see meta-analysis by Naragon-Gainey, 2010). Supporting this hypothesis, we found that panic disorder patients with agoraphobia (N = 491) but also a subgroup of patients with panic disorder without agoraphobia from a second multicenter clinical study (N = 30) reported significantly elevated levels of AS compared to a student control group (N = 279) (patient with PD/AG: M = 31.4, SD = 11.6; patients magnitudes that were potentiated during the first 60 seconds of exposure to the chamber (i.e., during attentive freezing) decreased just prior to escape. This decrease was even stronger in patients who escaped from the chamber during a self-reported panic attack (Richter et al., 2012), suggesting that this response pattern was even more pronounced for higher intensity of active avoidance/escape. These data are in line with results by Löw, Lang, Smith, and Bradley (2008) who showed that startle responses switched from potentiation during attentive freezing to inhibition during the stage of active response preparation. Following up on this research, Löw, Weymar, and Hamm (in press) more recently demonstrated that startle potentiation linearly increased with increasing proximity of the threat accompanied by fear bradycardia when individuals had no option for active avoidance (which is typically the case in classical fear conditioning designs). In contrast, startle response magnitudes were strongly inhibited and heart rate accelerated during circa strike when individuals were given the opportunity to actively avoid the upcoming threat (an aversive electrical stimulus in this experiment). Interestingly, the P3-component of the event-related brain potential to the startle-eliciting acoustic probe stimulus was also strongly attenuated when individuals had the option to
with PD without AG: \( M = 29.6, SD = 10.6 \); healthy controls: \( M = 18.6, SD = 8.9 \).

A second trait like dimension derived from biological models suggesting breathing-related symptoms to be the main source of fear initiating panic attacks and therefore a central component for the etiology of PD is fear of suffocation (Klein, 1993; Ley, 1985, 2005). Fear of suffocation has also been suggested to predict the number of reported panic symptoms, particularly during experimentally provoked panic attacks (Alius, Panné-Farré, Von Leupoldt, & Hamm, 2013; Taylor & Rachman, 1994). Interestingly, individuals with high levels of suffocation fear not only report more anxiety and show elevated autonomic arousal during a dyspneic challenge, but they also show “maladaptive” compensatory ventilatory behavior while breathing through increased resistive loads (Alius et al., 2013). Fear of suffocation was assessed using the suffocation subscale of the Claustrophobic Questionnaire (CLQ; see Radomsky, Rachman, Thordarson, McIsaac, & Teachman, 2001 for an updated version of this scale) in these studies. Supporting the hypothesis that fear of suffocation might also be a risk factor for developing a PD/AG, we found significantly elevated levels of suffocation fear in panic disorder patients with agoraphobia but not in a subgroup of patients from the second multicenter RCT study who were diagnosed with panic disorder without meeting the criteria for agoraphobia (patients with panic disorder with agoraphobia: \( M = 25.8, SD = 11.0 \); patients with panic disorder without agoraphobia: \( M = 10.5, SD = 7.6 \); healthy controls: \( M = 8.4, SD = 5.9 \)). These data suggest that both dimensional constructs might be associated with different aspects of the disorder and possibly with different patterns of defensive reactivity.

Suffocation fear predicted actual passive and active avoidance/escape in the BAT. Patients reporting clinically significant levels of suffocation fear (2 SDs above the mean of the control group) significantly more often avoided to enter the chamber or left it before exposure time had elapsed (84% of the passive avoiders and 77% of the active avoiders had suffocation fear levels that were 2 SDs above the mean). Moreover, suffocation fear was significantly related to the duration patients remained in the chamber. Suffocation fear was also significantly correlated (\( r = .51; p < .001 \)) with the severity of avoidance as assessed at baseline with the MI. In addition, suffocation fear was significantly related to reported anxiety and panic symptoms during exposure suggesting that this trait measure was related to the intensity of fear and avoidance in this specific situation of entrapment. In contrast to suffocation fear, reported anxiety sensitivity was not related to active and passive avoidance in the BAT (the distribution of patients with clinically significant levels of AS (2 SDs above the mean of the healthy control group) was 38%, 31.9%, and 35.9% of passive avoiders, active avoiders/escapers, and anxious completers, respectively). Moreover, while ASI scores were not related to self-reported avoidance behavior according to the MI (\( r = .07; \text{n.s.} \)), it was associated with reports of catastrophic thoughts (assessed with the agoraphobic cognitions questionnaire: \( r = .45; p < .001 \)), reported fear of bodily sensations (assessed with the body sensations questionnaire: \( r = .43; p < .001 \)), health worries (assessed with the Panic and Agoraphobia Scale: \( r = .47; p < .001 \)), general distress (assessed with the BSI; \( r = .44; p < .001 \)), and depressive mood (assessed with the Beck Depression Inventory; \( r = .30; p < .001 \)), suggesting that elevated anxiety sensitivity is more related to anxious apprehension and negative affect, rather than to avoidance. These findings were supported by the results of a logistic model of BAT avoidance behavior with multiple self-report measures (CLQ-SF, ASI, BDI, and BSI): only self-reported suffocation fear significantly predicted active (\( OR: 1.07, p < .001 \)) and passive avoidance behavior in the BAT (\( OR: 1.08, p < .001 \)), no other self-report measure was significant. Moreover, only reported suffocation fear but no other self-report measure significantly predicted self-reported avoidance as assessed by the MI total score (\( \beta = 0.44, p < .001 \)), supporting the specific association between suffocation fear and avoidance behavior.

Different patterns of defensive reactivity were not only associated with different dimensional trait-related self-report measures, but also with different genetic risk factors. In the MAC study, genetic data from 269 patients who participated in the BAT and for whom blood samples were available were analyzed. We investigated the influence of two candidate genes that are involved in serotonergic neurotransmission on patterns of defensive reactivity in the BAT. In a first step, we analyzed a common variant in the promoter region of the gene encoding monoamine oxidase A (MAOA)—an enzyme that metabolizes serotonin and norepinephrine. This polymorphism is a 30-bp variable number of tandem repeat (MAOA-uVNTR) affecting gene expression (Deckert et al., 1999). Long alleles (3.5, 4, and 5 repeats of the 30 base pairs) are associated with panic disorder in females (Deckert et al., 1999; Maron et al., 2005; Samochowiec et al., 2004). Patients with the high-risk variant gene showed stronger fear responses in the BAT, as indicated by significantly elevated heart rate and reports of higher anxiety during exposure (Reif et al., 2014). In addition, all but one patients reporting a panic attack in the chamber (33 out of 34) were high-risk genotype carriers leading to the overall assumption that patients carrying the MAOA-uVNTR risk variant were more prone to show strong acute fear reactivity when being confronted with a typical agoraphobic situation (in this case, being entrapped in a small dark chamber). Interestingly, Miller, Deakin, and Anderson (2000) found enhanced panic responses to breathing 5% CO\(_2\) but lessened anxiety ratings during anticipation of this task when 5-HT functioning was reduced by acute tryptophan depletion (ATD). In a similar way, serotonin reduction increases acquisition of active avoidance in rodents while elevated levels have the opposite effect (Beninger, 1989). Stimulated by this research, we investigated a serotonin receptor 1a gene (HTR1A) polymorphism in the group of 245 patients from the MAC-study who participated in the BAT. The G-allele in the transcriptional control region of the HTR1A increases the expression of the gene at the presynapase where the gene product functions as an autoreceptor and thus reducing serotonergic neurotransmission due to enhanced auto-inhibitory feedback. In line with previous animal data, we found significantly increased active avoidance/escape behavior in GG-genome carriers compared to CC carriers with GC carriers falling in between (see upper panel of Figure 3). This genetic modulation of active avoidance/escape behavior was also evident during exposure sessions of the standardized CBT. Duration of self-guided exposure was significantly shorter (particularly during the two most feared situations) in the GG carriers compared to the CC carriers (see Straube et al., 2014). These data strongly suggest that the serotonergic system is involved in circastrike defense. Reduction of 5 HT functioning seems to increase acute fear/panic during exposure and to facilitate escape behavior possibly mediated by the dIPAG.

In contrast to the serotonergic system, the corticotropin-releasing hormone (CRH) does not modulate acute fear and avoidance in the BAT but rather seems to be involved in the modulation of general distress and chronic anxious apprehension. We investigated allelic variation of the CRH receptor 1 (CRHR1) in a sample of 267 patients with PD/AG from the MAC study. We found that against other a single nucleotide polymorphism (SNP) of the CRH receptor 1 gene influences gene expression and was significantly
associated with the categorical diagnosis of panic disorder and defensive reactivity during the BAT (Weber et al., 2015). The risk allele carriers showed a reduced acute fear response and less active avoidance in the BAT task but reported more general distress and expressed more negative evaluations of their body symptoms, thus showing more chronic and generalized apprehension than acute fear or panic. Indeed, animal and human data suggest that CRH is critical for expression of sustained anxiety but not phasic fear (Davis, Walker, Miles, & Grillon, 2010).

Summarizing our observations so far, we found evidence that dimensional trait-like measures as well as genetic markers that are associated with PD/AG might be related to different components (i.e., acute fear/panic as an instance of circa-strike defense and anxious apprehension reflecting postcounter defense) that define the categorical diagnosis of the disorder (see lower panel of Figure 3 for a summary). In the next step, we explore whether this dimensional approach using the dynamics of defensive reactivity as a new tool for describing patients who all received the same categorical diagnosis—PD/AG—might be useful for tailoring exposure therapy in a way to improve outcome. Numerous variants of cognitive-behavioral therapy (CBT) for panic disorder with and without agoraphobia have been shown to be efficacious and are therefore regarded as a first-line treatment (for a meta-analyses, see Sánchez-Meca, Rosa-Alcázar, Marín-Martínez, & Gómez-Conesa, 2010). Despite the documented efficacy of CBT for PD/AG (Otto, Pollack, & Maki, 2000), several core questions remain, particularly about the mechanisms of action and essential contents and ingredients of the therapy. In the next section, we therefore take the first step linking different components of defensive reactivity to therapy outcome measures, trying to identify how different components of the disorder might respond in a specific way to circumscribed elements of the intervention.

### Relating Defensive Reactivity to Treatment Outcome

In a first multicenter randomized controlled trial, 369 patients with PD/AG were treated and followed up for 6 and 24 months (see Gloster et al., 2011, 2014). Patients were randomized to two manual-based variants of CBT or a wait list control (WL; N = 68) and were treated twice weekly for 12 sessions. CBT variants were identical in content, structure, and length except for implementation of exposure in situ. In one variant (T+; N = 163), exposure in situ exercises were accompanied by the therapist outside the therapy room; in the other variant (T−; N = 138), exposure exercises were planned and discussed with the patient, but exercises outside the therapy room were not accompanied by the therapist. Overall, this treatment was very effective in both treatment conditions (effect sizes varied from −0.5 to −2.5 in all primary outcome variables from pre to post and further improved from post to 6 months follow-up; Gloster et al., 2011). A second multicenter randomized controlled trial followed up on this study. In this study, 124 patients with PD/AG were treated using two manual-based variants of CBT for 12 sessions. Again, variants were identical in content, structure, and length except with regard to the implementation of exposure in vivo. In one variant (T+; N = 61), exposure treatment was comparable to the T+ variant from the first clinical trial. In the other variant (T+L; N = 63), exposure in vivo exercises were also accompanied by the therapist, but in addition, patients were instructed to provoke bodily symptoms during exposure exercises (e.g., by doing a hyperventilation exercise). No WL control group was included in this study. Again, both treatment conditions were overall effective in this second treatment study. Treatment effects, however, were systematically modulated by avoidance behavior assessed prior to therapy. We collected behavioral data from the BAT for 397 patients with PD/AG who were allocated to the active treatment conditions in both clinical trials. We found significantly larger attrition rates in those 116 PD/AG patients who showed active or passive avoidance behavior (i.e., either did not enter the chamber or escaped prematurely) in the standardized BAT prior to therapy with nearly twice as many dropouts (N = 35; 30.2%) as compared to the 281 patients who did not show any avoidance behavior (N = 50; 17.8%; $\chi^2 = 7.48$, $p < .01$). Interestingly, patients who showed active or passive avoidance behavior during the initial BAT had better therapy outcome in case they completed the treatment. This effect was evident in both clinical trials. The left panel of Figure 4 presents changes in one outcome measure (Panic and Agoraphobia Scale [PAS]; Bandelow, 1995—a 13-item questionnaire that measures self-reported severity of panic attacks, avoidance, anticipatory anxiety, disability, and worries about health) separately for patients who showed active or passive avoidance in the BAT prior to treatment or not. Larger improvements were found for patients showing high avoidance tendencies compared to patients with no avoidance in the BAT but only if the therapist accompanied the patients during exposure exercises outside the therapy room (avoidance treatment variant $F(1, 222) = 4.68$, $p < .05$). This pattern of results was replicated in the second clinical trial (see right panel of Figure 4). Patients showing avoidance behavior prior to treatment profited more from exposure exercises. In the second trial, there were no differences between the two variants because the therapist accompanied the patient during exposure exercise in both variants.

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**Figure 3.** A: Rate of active avoidance/escape from the dark room according to the genotype of the serotonin receptor 1 a gene (HRTR1A). The G-allele increases receptor expression at the presynapse and thereby reduces serotonergic neurotransmission. B: A descriptive model of the associations between different components of defensive reactivity and trait-like dimensions of reported fear and genetic risk markers for fear and anxiety.
(avoidance $F(1, 82) = 6.24; p < .05$; avoidance x treatment variant $F(1, 82) = 0.46; p = .50$). Comparable results were also obtained after controlling for baseline differences in the PAS scores. The current data provide first evidence that behavioral avoidance measured in a standardized situation, as one component of defensive reactivity, is related to the outcome of CBT. Even more important, there is an interaction between avoidance behavior prior to therapy and the effect of active ingredients of CBT. Exposure exercises outside the therapy room seem to be particularly effective for patients with high avoidance disposition when the therapist actively accompanies them. This variant of active exposure is not as relevant if patients do not show very strong tendencies for active or passive avoidance prior to therapy. For those patients, it is equally effective to plan and discuss exposure exercises with them and then instruct them to do the exposure exercises by themselves.

Conclusions

Consistent with the goals of the RDoC initiative, we tried to develop an interdisciplinary approach conceptualizing the psychopathology of the categorical diagnosis—PD/AG—in terms of the dimensional construct defensive reactivity to approaching threat. Using the defense cascade defensive reactivity model derived from behavioral neuroscience research with animals and humans, we proposed a dynamic view stating that defensive responses vary on a dimension of threat imminence. Moreover, we presented evidence that these different defensive behaviors are related to different neural circuits in the brain. In the next step, we linked this model about behavior–brain relationships to clinical problems. We report evidence showing that panic attacks can be considered as fear responses to acute threat with the urge for active avoidance/escape when threat stimuli from inside the body are imminent. We found that this component of defensive reactivity is related to the serotonergic system and responds better to exposure treatment if the therapist guides the patient throughout the exposure exercises in vivo. A different component of the clinical problem, anxious apprehension to potential threat—characterized by attentive freezing during postencounter defense—seems to be related to general distress and depressive mood, as well as to genetic modulations within the HPA axis and is activated to more proximal threat. Whether increased attentive freezing can also be related to therapy outcome or specific components of CBT (e.g., cognitive strategies) is still an open question.

References

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