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Anticipating agoraphobic situations: the neural correlates of panic disorder with agoraphobia

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6 Department of Clinical Radiology, University of Münster, Münster, Germany
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Background. Panic disorder with agoraphobia is characterized by panic attacks and anxiety in situations where escape might be difficult. However, neuroimaging studies specifically focusing on agoraphobia are rare. Here we used functional magnetic resonance imaging (fMRI) with disorder-specific stimuli to investigate the neural substrates of agoraphobia.

Method. We compared the neural activations of 72 patients suffering from panic disorder with agoraphobia with 72 matched healthy control subjects in a 3-T fMRI study. To isolate agoraphobia-specific alterations we tested the effects of the anticipation and perception of an agoraphobia-specific stimulus set. During fMRI, 48 agoraphobia-specific and 48 neutral pictures were randomly presented with and without anticipatory stimulus indicating the content of the subsequent pictures (Westphal paradigm).

Results. During the anticipation of agoraphobia-specific pictures, stronger activations were found in the bilateral ventral striatum and left insula in patients compared with controls. There were no group differences during the perception phase of agoraphobia-specific pictures.

Conclusions. This study revealed stronger region-specific activations in patients suffering from panic disorder with agoraphobia in anticipation of agoraphobia-specific stimuli. Patients seem to process these stimuli more intensively based on individual salience. Hyperactivation of the ventral striatum and insula when anticipating agoraphobia-specific situations might be a central neurofunctional correlate of agoraphobia. Knowledge about the neural correlates of anticipatory and perceptual processes regarding agoraphobic situations will help to optimize and evaluate treatments, such as exposure therapy, in patients with panic disorder and agoraphobia.

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Key words: Agoraphobia, anticipation, functional magnetic resonance imaging, insula, panic, ventral striatum, Westphal paradigm.

Introduction

Agoraphobia is characterized as a phobic anxiety in situations where escape can be difficult or embarrassing. Examples of these situations include wide-open spaces, crowded places, shopping malls and public transportation. Patients often anticipate panic attacks or panic-like symptoms, such as a pounding heart or accelerated heart rate, sweating, a feeling of choking, chest pain, dizziness and a fear of dying. Panic disorder and agoraphobia, with a 12-month prevalence of 1.8% and 2%, belong to the most prevalent group of mental disorders – anxiety disorders (Wittchen et al. 2011). More than a third of patients with panic disorder also suffer from agoraphobia (Kessler et al. 2006).

The neural processing of aversive and anxiety-related stimuli relies on the so-called ‘fear network’
(Gorman et al. 2000). As core regions, the amygdala, hippocampus (Sakai et al. 2005; van den Heuvel et al. 2005) and insula (Nagai et al. 2007; Wittmann et al. 2011) show increased activation in patients with panic disorder with and without agoraphobia. Unfortunately, most previous studies lack information concerning the coincidence of agoraphobia and therefore insights into neural networks specific to agoraphobia are limited (Dresler et al. 2012). Arguably, the neural response of individuals suffering from panic disorder with agoraphobia to the anticipation of, and the confrontation with, agoraphobic situations is equivalent to in vivo exposure. Since in vivo exposure is a first-choice psychotherapeutical intervention for panic disorder with agoraphobia (Gloster et al. 2011), measuring these neural reactions is a highly relevant task. In addition to this, despite the fact that anticipatory anxiety often impairs the daily life of patients to a much greater extent than the anxiety in an agoraphobic situation itself, the anticipatory processes of agoraphobia-related stimuli have not been the focus of large-scale neuroimaging studies. In consequence, the specifically altered activity of the different areas participating in neural processes associated with anticipation and perception of aversive and agoraphobia-related stimuli has not been identified.

Studies investigating the anticipation of aversive and anxiety-related stimuli have found an increased activation in the amygdala, anterior cingulate cortex (Ueda et al. 2003) and the insula (Simmons et al. 2006; Wittmann et al. 2011) as core regions of the neural fear network. (For a more detailed overview of symptom provocation in anxiety disorders, please refer to Wittmann et al. 2011.) The ventral striatum (VS) was found to be crucial during the anticipation and identification of stimuli with emotional significance (Phillips et al. 2003; Lorberbaum et al. 2004; Herwig et al. 2007). Recent studies have shown the mediating role of the VS in anticipatory processes of both appetitive and aversive stimuli in healthy volunteers (Liu et al. 2011; Yang et al. 2012) and anxiety disorders (Guyer et al. 2012).

Therefore, we developed an agoraphobia-specific stimuli set and established a functional magnetic resonance imaging (fMRI) paradigm including an anticipation phase. In honour of Carl Westphal, who first described agoraphobia as a distinct disorder (Westphal, 1871), we named this paradigm the ‘Westphal paradigm’ (Wittmann et al. 2011). A pilot study revealed neurofunctional activations in patients suffering from panic disorder with agoraphobia, including amygdala, insula and parahippocampal areas. The paradigm also produces reliable self-report data and its psychometric properties meet the necessary quality requirements with regard to criterion and construct validity as well as reliability (Wittmann et al. 2011). These aspects indicate that the Westphal paradigm can be used to further characterize the neurofunctional basis of panic disorder with agoraphobia. In the present study we report the comparison of a large group of patients, matched with healthy participants, to demonstrate disorder-specific neural processes related to the anticipation and perception of agoraphobia-specific stimuli.

We hypothesized that patients who suffer from panic disorder with agoraphobia would show altered neural processes when anticipating and perceiving agoraphobia-specific stimuli compared with matched healthy controls. While we expected larger blood oxygen level dependence (BOLD) responses in areas of the fear network including the amygdala and insula (Sakai et al. 2005; van den Heuvel et al. 2005; Nagai et al. 2007; Holzschneider & Mulert, 2011; Wittmann et al. 2011) during both the anticipation and perception of agoraphobia-specific stimuli, we hypothesized heightened activation during the anticipation of agoraphobia-specific stimuli in the VS (Jensen et al. 2003; Herwig et al. 2007; Schiller et al. 2008).

Method

Participants

Volunteers were recruited from the participating universities and fMRI centres in Aachen, Berlin-Charité, Berlin-Adlershof, Dresden and Münster. All patients took part in the German multicentre trial, ‘Mechanisms of Action in CBT’ (MAC) (Gloster et al. 2009), and therefore met the diagnostic criteria for panic disorder with agoraphobia (Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; DSM-IV-TR) as determined by a standardized computer-administered personal Composite International Diagnostic Interview (CAPI-WHO-CIDI; DIA-X-CIDI version; Wittchen & Pfister, 1997) conducted by trained professionals. No patients with isolated panic disorder, isolated agoraphobia, or panic attacks were included in the study. Additionally, all patients had a score ≥ 18 on the structured interview guide for the Hamilton Anxiety Scale (HAMA; Shear et al. 2001) and a score ≥ 4 on the Clinical Global Impressions Scale (Guy, 1976). Patients were aged between 18 and 65 years old and had not received psychopharmacological treatment for at least 4 weeks before the beginning of the study, nor had they taken part in any psychotherapeutic treatment. Other exclusion criteria were co-morbid psychotic or bipolar I disorder, current alcohol dependence/current abuse of or dependence on psychoactive substances, current suicidal ideations, borderline personality disorder,
significant abnormalities in electroencephalography (EEG), electrocardiography (ECG), routine clinical chemistry or haematology. Handedness was measured by the Edinburgh Inventory (Oldfield, 1971). Colour vision was assessed with the Ishihara colour blindness test (Ishihara, 1917). Healthy controls had to pass the same diagnostic procedure; had to have never fulfilled criteria for a mental disorder; and were individually matched for age, gender, handedness, smoking status and education level of the included patients. All participants additionally did not meet the MRI contraindications (e.g. ferromagnetic material or cardiac pacemakers). The diagnostic procedure was accomplished within a maximum of 7 days prior to the scan. The age of the patients and healthy controls did not differ ($p=0.825$), values of the HAMA (Shear et al. 2001) differed significantly ($p<0.001$); however, values for the Mobility Inventory (MI; Chambless et al. 1985) were not available for healthy volunteers (see Table 1). All participants were asked to refrain from smoking for at least 4 h prior to the scan. Out of 369 patients who met these criteria, a total of 89 patients underwent fMRI before any therapeutic intervention took place. Therefore anxiety regarding the scanner environment was relatively high in most patients. An empathic step-by-step explanation of the procedure and therefore enabling a maximum of control helped them to cope with this aversive experience. However, five patients refused to participate in the fMRI session because their anxiety levels were too high. Scans of 12 patients were discarded due to excessive head movements of more than twice the voxel size ($n=4$) or due to the joint multicentre criteria of data quality ($n=8$). For the latter joint quality control (Kircher et al. 2013) a percent signal fluctuation index (PSF; Stocker et al. 2005) and a signal-to-fluctuation noise ratio (SFNR; Friedman & Glover, 2006) were calculated. The threshold for data exclusion was a value greater than 2.5 s.d.s on the PSF and SFNR. For the control group we included 72 matched healthy volunteers who were separately recruited according to the matching criteria of each already recruited patient. All participants gave their written informed consent. The clinical trial was approved by the Ethics Committee of the Medical Faculty of the Technische Universität Dresden (EK 164082006). The neuroimaging study was approved by the ethics committees of all participating sites. All approvals were made according to the Declaration of Helsinki.

### Experimental design

We used the Westphal paradigm (as shown in Fig. 1), which had already been evaluated in a pilot study (Wittmann et al. 2011). It is composed of 48 agoraphobia-related pictures specifically generated for this paradigm (e.g. pictures of means of public transportation, images of crowds, heights, automobiles, dense situations, etc.). Pictures were taken according to the examples of agoraphobic situations from the DSM-IV as well as from the interviews with patients (with panic disorder and agoraphobia). After being selected by experts, the remaining pictures were rated by patients and matched healthy controls using the Self-Assessment Manikin Scale (Bradley & Lang, 1994). Only pictures with rating values which allowed us to discriminate between patients and controls were included in the paradigm (Wittmann et al. 2011). Furthermore, 48 neutral pictures were taken from the International Affective Picture System (Lang et al. 1997). Half of the 96 pictures were preceded by an anticipatory stimulus that indicated the category of the upcoming picture using the words ‘neutral’ and ‘panic’. The other half of the set of pictures was preceded by a non-specific anticipation stimulus, i.e. a random combination of characters (‘DGHNTFJ’). Thus, 24 pictures were presented in each condition. The picture sequence was randomized for each participant. Presentation duration for each picture was 2000 ms and 250 ms for anticipatory stimuli. Both were separated by the presentation of a fixation cross in order to minimize artifacts due to eye movements with a variable duration of between 2 and 4 s. Inter-trial intervals were variable with a duration of between 2 and 6 s. The complete experiment duration

<table>
<thead>
<tr>
<th>n</th>
<th>Patients with panic disorder with agoraphobia</th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (s.d.)</td>
<td>36.7 (11.2)</td>
<td>36.2 (11.2)</td>
</tr>
<tr>
<td>Left-handed, n</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Smoking, n</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Education, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13 years</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>10 years</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>9 to 10 years</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Mean HAMA (s.d.)</td>
<td>23.1 (6.3)*</td>
<td>2.0 (2.3)</td>
</tr>
<tr>
<td>Mean MI (s.d.)</td>
<td>2.8 (0.8)</td>
<td>–</td>
</tr>
</tbody>
</table>

s.d., Standard deviation; HAMA, Hamilton Anxiety Scale; MI, Mobility Inventory.

* Age of patients and healthy controls did not differ ($p=0.825$).

* Mean value was significantly different from that of the control group ($p<0.001$).
was approximately 15 min. Presentation version 11.0 (Neurobehavioral Systems, USA) was used to present the stimuli. During the fMRI session participants were instructed to pay attention to the picture content. They were requested to try to experience the presented situation and to imagine being in it at that moment. Furthermore, they were asked to pay attention to the anticipatory stimulus and its predictive content before picture presentation. Attention to the paradigm and its pictures was assured by the request to push a button each time a picture was presented.

Self-report data

In order to estimate the validity of the agoraphobia-specific and neutral pictures all stimuli were rated in terms of agoraphobic anxiety, arousal and valence after the scanning session on a modified Self-Assessment Manikin Scale (Bradley & Lang, 1994). Ratings were analysed using a 2×2 analysis of variance for repeated measures [group (patients/controls)×picture type (agoraphobia/neutral)] with group as the between-subject factor and picture type as the within-subject factor. Post-hoc t tests were used to determine group differences. Associations between anxiety ratings and clinical data were achieved by calculating Pearson’s correlations.

Functional imaging

Assurance of data quality was in line with the procedure within the joint multicentre quality control (Kircher et al., 2013). Functional imaging was performed on 3-T General Electric Healthcare (Berlin), 3-T Siemens Trio (Dresden) and 3-T Philips Achieva (Münster and Aachen) scanners. During each fMRI session, 446 volumes were acquired using the following parameters to minimize artifacts and signal loss: echo planar imaging (EPI) pulse sequence; echo time =30 ms; repetition time=2 s; flip angle=90°; matrix...
size=64×64; voxel size=3.6×3.6×3.8 mm; 30 slices without an intersection gap were collected, aligned parallel to the anterior commissure-posterior commissure (AC-PC) line, interleaved and in ascending order. Data analysis was carried out using Statistical Parametric Mapping (version SPM8, http://www.fil.ion.ucl.ac.uk/spm). Preprocessing consisted of correcting slice-time acquisition delay and movement (by realigning to the individual mean EPI), spatial normalization to the standard EPI template and spatial smoothing with 8 mm full width at half-maximum. The first five volumes of each time series were discarded to avoid non-steady-state effects caused by T1 saturation. The BOLD response was analysed in the context of the general linear model using a two-level saturation. The BOLD response was modelled as explanatory conditions following con-

In the anticipation phase, we also de-
ned volumes of interest

 Associations between ratings of the agoraphobia-specific pictures, clinical measure of agoraphobic avoidance behaviour (using the MI; Chambless et al. 1985) as well as neural activation (using mean parameter estimates extracted from the VOIs) were computed using Pearson’s correlations within SPSS (IBM, USA).

Results

Self-report data

Ratings of agoraphobia-specific and neutral pictures revealed a significant main effect of group ($F_{1,137} = 106.97, p<0.001, \eta^2_p = 0.438$) and picture type ($F_{1,137} = 245.11, p<0.001, \eta^2_p = 0.641$) and a group×picture type interaction ($F_{1,137} = 166.98, p<0.001, \eta^2_p = 0.549$). Post-hoc $t$ tests indicated that patients rated the agoraphobia-specific pictures more anxiety inducing ($t_{137} = 12.09, p<0.001$), more unpleasant ($t_{137} = 6.12, p<0.001$) and more arousing ($t_{137} = 9.79, p<0.001$) than healthy controls, while there were no group differences for the ratings of neutral pictures (all $p$ values $>0.011$) (see online Supplementary Table S1).

The relationship between the anxiety ratings of the agoraphobia-specific pictures and symptom severity was assessed within the patient group. We found significant positive correlations between anxiety ratings and the MI (unaccompanied) score ($r = 0.47, p<0.001$).

fMRI

Anticipation phase

When the patients were anticipating agoraphobia-related compared with neutral stimuli, an increased activation in the bilateral VS and left insula was observed (left VS: $T = 2.42, x = -18, y = 5, z = -8, p_{SVC\ for\ VS\ VOI} = 0.072$; right VS: $T = 2.7, x = 15, y = 5, z = -8, p_{SVC\ for\ VS\ VOI} = 0.039$; left insula: $T = 4.57, x = -39, y = 17, z = -8, p_{SVC\ for\ insula\ VOI} = 0.003$) while the healthy control group showed no significant activation or deactivation. There was no activation of the amygdala during the anticipation of agoraphobia-specific stimuli.

Comparing the activations of both groups, patients displayed stronger activation in the bilateral VS (see Fig. 2) and left insula (left VS: $T = 3.5, x = -18, y = 5, z = -8, p_{SVC\ for\ VS\ VOI} = 0.004$; right VS: $T = 4.0, x = 15, y = 8, z = -8, p_{SVC\ for\ VS\ VOI} = 0.001$; left insula: $T = 4.2, x = -30, y = 26, z = 10, p_{SVC\ for\ insula\ VOI} = 0.005$). The hypothesized stronger activation in the amygdala of patients compared with healthy controls was not observed. There were neither significant group differences, nor within-group activations or deactivations.

Associations between ratings of the agoraphobia-specific pictures, clinical measure of agoraphobic avoidance behaviour (using the MI; Chambless et al. 1985) as well as neural activation (using mean parameter estimates extracted from the VOIs) were computed using Pearson’s correlations within SPSS (IBM, USA).
Fig. 2. Activation in the ventral striatum (bilateral) is stronger in patients than in healthy controls when anticipating agoraphobia-specific stimuli and mean parameter estimates correlate with the values of anxiety ratings of 68 patients for agoraphobia-specific stimuli.
in the whole-brain analyses (FWE whole brain-corrected) outside the predefined VOIs.

Extracting mean parameter estimates from the VS VOI and correlating these values with the anxiety ratings showed significant positive correlations for the patient group (right VS: $r=0.24$, $p=0.041$; left VS: $r=0.27$, $p=0.021$), as displayed in Fig. 2. Mean parameters of the left insula VOI were positively correlated with the values of the MI (unaccompanied) ($r=0.29$, $p=0.015$).

**Picture phase (agoraphobia-specific pictures v. neutral pictures)**

Contrary to our initial hypothesis, there were no significant group differences when comparing agoraphobia-specific pictures with neutral pictures in the a priori-defined areas of the amygdala and insula (after small volume correction) nor in the whole-brain analyses (FWE whole brain corrected $p>0.2$).

However, the patient group displayed a significant activation in the bilateral insula (left insula: $T=5.3$, $x=-30$, $y=20$, $z=-20$; $p_{SVC}$ for insula VOI$<0.001$; right insula: $T=4.44$, $x=33$, $y=17$, $z=-20$; $p_{SVC}$ for insula VOI=0.004) while perceiving agoraphobia-specific compared with neutral stimuli, but no significant group difference was observed in this region.

In the whole-brain analyses both healthy controls and patients showed neuronal responses elicited by agoraphobia-specific compared with neutral pictures in areas involved in the processing of spatial information including parahippocampal areas and occipital areas as well as areas associated with panic disorder and agoraphobia such as the posterior cingulum and precuneus (see Table 2).

**Discussion**

This is the first study comparing the neural activations of patients suffering from panic disorder with agoraphobia and healthy controls to agoraphobia-specific stimuli. We found an increased activation in the insula and the VS in patients compared with healthy controls during the anticipation of agoraphobia-specific stimuli, while no group differences were found during the perception phase.

From a clinical perspective we know that patients often report much higher anxiety before entering an agoraphobic situation compared with being in the situation itself (Heilig-Lang et al. 2012). Our finding of higher BOLD responses in the insula and VS only in anticipation but not in perception of agoraphobia-related stimuli in patients supports this important differentiation between anticipation and event. The insula has been shown to be involved in the processing of anticipatory anxiety (Boshuisen et al. 2002; Simmons et al. 2006; Herwig et al. 2007) and salience (Menon & Uddin, 2010). Within this salience network model, the insula is relevant for (a) the detection of salient events, (b) switching access to attention and working memory resources when salient events are detected, (c) the modulation of autonomic reactivity to the salient stimuli, and (d) channelling fast access to the motor system. These functions of the insula might be even more important in patients with high agoraphobic avoidance behaviour, as suggested by the positive correlation between heightened anticipatory insula activation with the MI questionnaire. Arguably, our results additionally suggest an increased activation of the insula in patients during their day-to-day life. Thus, whenever they anticipate being confronted with an agoraphobic situation, an increased insula activity may cause increased perception of internal body symptoms (such as heartbeat, respiration, etc.) that may be followed by a higher probability of panic attacks (Delgado et al. 2009). The insula (as a cortical region relevant for processing interoceptive signals) would play a crucial role in the neural fear circuit and in the vicious circle of panic attacks, respectively.

The VS is known to be relevant for the evaluation of the individual salience of stimuli while planning behavioural reactions (Horvitz, 2002; Jensen et al. 2003; Delgado et al. 2009; Heinz & Schlagenhauf, 2010; van den Heuvel et al. 2011). The increased activation of the VS may represent pathological processes, such as exploring the environment for potential threats, evaluating, and preparing actions. Arguably, this mechanism is hypersensitive in patients suffering from anxiety disorders such as agoraphobia (Paulus & Stein, 2006; Simmons et al. 2006). Moreover, the VS seems to affect avoidance learning with regard to an aversive event (Jensen et al. 2003; Schiller et al. 2008; Delgado et al. 2009) or during the planning of actions (van den Heuvel et al. 2011), processes that are important for the development of avoidance behaviour towards agoraphobic situations. Finally, the finding of the correlation between anxiety ratings of agoraphobia-specific stimuli and activation in the bilateral VS supports the hypothesis that there is a relationship between dysfunctional VS activation and the clinical impairment of agoraphobia.

During the perception of agoraphobia-specific compared with neutral pictures patients and healthy controls activated areas involved in the processing of spatial information like the parahippocampal place area and occipital cortex, indicating that both groups processed the spatial and contextual information from the agoraphobia-specific stimuli.
Table 2. Neural activations of patients and healthy controls during the picture phase (agoraphobia-specific vs. neutral pictures) sorted by lobes and subordinated cerebral structures

<table>
<thead>
<tr>
<th>Sample</th>
<th>Lobe</th>
<th>Cerebral structure</th>
<th>BA</th>
<th>HS</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>T</th>
<th>p(FWE-cor)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Superior frontal gyrus</td>
<td>8</td>
<td>L</td>
<td>−33</td>
<td>14</td>
<td>55</td>
<td>5.22</td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Middle frontal gyrus</td>
<td>8</td>
<td>L</td>
<td>−24</td>
<td>20</td>
<td>46</td>
<td>5.12</td>
<td>0.029</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior frontal gyrus</td>
<td>47</td>
<td>R</td>
<td>30</td>
<td>17</td>
<td>−23</td>
<td>5.74</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior frontal gyrus</td>
<td>47</td>
<td>L</td>
<td>−48</td>
<td>26</td>
<td>−17</td>
<td>5.71</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medial frontal gyrus</td>
<td>11</td>
<td>L</td>
<td>0</td>
<td>62</td>
<td>−11</td>
<td>5.42</td>
<td>0.011</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Precuneus</td>
<td>7</td>
<td>L</td>
<td>−12</td>
<td>−82</td>
<td>58</td>
<td>8.90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Precuneus</td>
<td>7</td>
<td>R</td>
<td>6</td>
<td>−46</td>
<td>46</td>
<td>8.03</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Middle temporal gyrus</td>
<td>20/21</td>
<td>R</td>
<td>27</td>
<td>23</td>
<td>43</td>
<td>5.06</td>
<td>0.045</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medial parietal lobule</td>
<td>40</td>
<td>L</td>
<td>−45</td>
<td>−37</td>
<td>43</td>
<td>4.99</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Middle occipital gyrus</td>
<td>19/37</td>
<td>L</td>
<td>−45</td>
<td>−82</td>
<td>−11</td>
<td>7.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Middle temporal gyrus</td>
<td>39</td>
<td>R</td>
<td>45</td>
<td>−79</td>
<td>25</td>
<td>12.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Middle frontal gyrus</td>
<td>8</td>
<td>R</td>
<td>27</td>
<td>23</td>
<td>43</td>
<td>5.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medial parietal lobule</td>
<td>37</td>
<td>R</td>
<td>27</td>
<td>−46</td>
<td>−11</td>
<td>11.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Superior occipital gyrus</td>
<td>19</td>
<td>R</td>
<td>39</td>
<td>−85</td>
<td>28</td>
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MNI, Montreal Neurological Institute; BA, Brodmann area; HS, hemisphere; p(FWE-cor), family-wise error-corrected p < 0.05; L, left; R, right.
However, contrary to our initial hypothesis, we could not detect any group differences in areas of the classical fear network (including the amygdala) in response to agoraphobia-related stimuli. On the behavioural level, agoraphobia-specific pictures were rated to be more anxiety-inducing than neutral pictures by patients compared with healthy controls, and these ratings were correlated with clinical scores and the magnitude of the clinical impairment. Therefore, the pictures were likely to be differently perceived depending on group status (patients vs. controls). The failure to detect activation differences on the neuronal level during the perception phase might be related to limited realization of stimulus presentations specific for the individual anxiety-inducing situation of each individual patient.

This result may support the idea that the amygdala is a switch point in the neural fear network during the evaluation of threats in the environment, which (dependent on the strength of its anxiety-inducing content) is not necessarily activated more strongly in patients (compared with healthy controls) when contrasting pictures of various agoraphobia-specific situations with neutral pictures. The role of the amygdala as a pivotal structure within the distributed fear network, but not necessarily as the single indicator of an anxious reaction, is in line with Gorman et al. (2000). This theory postulates that reciprocal connections of the amygdala disseminate information for the coordination of autonomic and behavioural response by connections to regions participating in processing and evaluation of sensory information, e.g. the sensory thalamus and insula. From this holistic perspective, the amygdala is an important structure for the perception processes of anxiety-related stimuli, such as the evaluation of relevance, valence and salience, but it has not to be classified as a more significant part of the fear network than other regions (Holzschneider & Mulert, 2011; Dresler et al. 2012).

Our results have to be interpreted within the context of a range of limitations. We are unable to separate the activation patterns in patients suffering from panic disorder with agoraphobia from comparable findings in patients suffering from other mental disorders, such as, for instance, specific phobias (Etkin & Wager, 2007), social anxiety disorder (Lorberbaum et al. 2004; Guyer et al. 2008) or panic disorder without agoraphobia. A comparison of the neural response patterns of these patient groups would be worth pursuing in future research. Moreover, the realization of this large data sample was only possible using several tomographies, which may have caused unwanted variance. We controlled this by calculating a joint multicentre quality control (Kircher et al. 2013) as a criterion for data inclusion, and we controlled for variance of each study site in each analysis. However, we did not find significant differences between study sites. Furthermore, we could not control to what extent participants were able to perceive presented stimuli as real. Therefore induction of emotion and neural activity may differ between subjects. The use of the word ‘panic’ as the anticipatory cue in our paradigm might have had an effect per se on increasing arousal, especially in the patient group. Although this might have contributed to the anticipatory effect, the observed correlation between the striatal activation during anticipation and the subjective anxiety ratings of the agoraphobic pictures indicates that anticipatory activation was related to the anticipated agoraphobic pictures that were rated as more anxiety-inducing by patients compared with healthy controls. Finally the MRI device itself might be an anxiety-inducing situation – especially for patients who suffer from panic disorder – which may affect the neural activity (e.g. baseline activation due to anxious arousal induced by being in this situation) or result in a sample bias despite sample characteristics being comparable with the overarching treatment study (Gloster et al. 2011) (HAMA\text sub{MRI-sample}: mean=23.1, S.D.=6.3; MI\text sub{MRI-sample}: mean=2.8, S.D.=0.8 v. HAMA\text sub{treatment-sample}: mean=24.1, S.D.=5.2; MI\text sub{treatment-sample}: mean=3.0, S.D.=0.9).

In summary, our study provides evidence for different neural processing in patients with panic disorder with agoraphobia with regard to anticipation in comparison with the perception of agoraphobia-related stimuli in the VS and insula. This finding may indicate a neural correlate for anticipatory anxiety, which is often reported as a more impairing burden for patients than the fear itself experienced in agoraphobic situations, and might go hand in hand with a heightened attention to internal panic-associated body symptoms and an intensified evaluation of the environment for aversive conditions.

From a therapeutical perspective, we know that both frequency and duration of in vivo exposure increase when a therapist accompanies and supports the patient during confrontation with agoraphobic situations. In other words, overcoming anticipatory anxiety may be the most difficult first step in treatment, ensuring that the patient profits from the most relevant feature of his or her treatment regimen: the exposure to agoraphobic situations (Gloster et al. 2011). The investigation of neural plasticity in brain structures sensitive to, for example, such psychotherapeutical treatments or new approaches like repetitive transcranial magnetic stimulation (Zwanzger et al. 2009) will be the focus of future studies and might improve the therapeutical conditions for patients suffering from panic disorder with agoraphobia and other anxiety disorders.
Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291713003085.

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Principal investigators (PIs) with respective areas of responsibility in the MAC study are V. Arolt (Münster: overall MAC programme coordination), H. U. Wittchen [Dresden: PI for the randomized clinical trial (RCT) and manual development], A. Hamm (Greifswald: PI for psychophysiology), A. L. Gerlach (Münster: PI for psychophysiology and panic subtypes), A. Ströhle (Berlin: PI for experimental pharmacology), T. Kircher (Marburg: PI for functional neuroimaging) and J. Deckert (Würzburg: PI for genetics). Additional site directors in the RCT component of the programme are G. W. Alpers (Würzburg), T. Fydrich and L. Fehm (Berlin-Adlershof) and T. Lang (Bremen).

All PIs take responsibility for the integrity of the respective study data and their components. All authors and co-authors had full access to all study data. Data analysis and manuscript preparation were completed by the authors and co-authors of this article, and they take responsibility for manuscript accuracy and content.


The RCT 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-Westfälische Hochschule University Aachen (EK 073/07). The experimental pharmacology study was approved by the Ethics Committee of the state of Berlin (EudraCT: 2006-00-4860-29). The study was registered with ISRCTN (no. ISRCTN80046034).

Declaration of Interest

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V.A. is a member of advisory boards and/or gave presentations for the following companies: AstraZeneca, Janssen-Organon, Eli Lilly, Lundbeck, Pfizer, Servier and Wyeth. He also received grants from Astra-Zeneca, Lundbeck and Wyeth. He chaired the committee for the ‘Wyeth Research Award Depression and Anxiety’. These co-operations have no relevance to the work covered in this paper.

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References


Neural correlates of agoraphobia


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