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Scary symptoms? Functional magnetic resonance imaging evidence for symptom interpretation bias in pathological health anxiety

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Abstract Patients with pathological health anxiety (PHA) tend to automatically interpret bodily sensations as sign of a severe illness. To elucidate the neural correlates of this cognitive bias, we applied an functional magnetic resonance imaging adaption of a body-symptom implicit association test with symptom words in patients with PHA ($n = 32$) in comparison to patients with depression ($n = 29$) and healthy participants ($n = 35$). On the behavioral level, patients with PHA did not significantly differ from the control groups. However, on the neural-level patients with PHA in comparison to the control groups showed hyperactivation independent of condition in bilateral amygdala, right parietal lobe, and left nucleus accumbens. Moreover, patients with PHA, again in comparison to the control groups, showed hyperactivation in bilateral posterior parietal cortex and left dorsolateral prefrontal cortex during incongruent (i.e., harmless) versus congruent (i.e., dangerous) categorizations of body symptoms. Thus, body-symptom cues seem to trigger hyperactivity in salience and emotion processing brain regions in PHA. In addition, hyperactivity in brain regions involved in cognitive control and conflict resolution during incongruent categorization emphasizes enhanced neural effort to cope with negative implicit associations to body-symptom-related information in PHA. These results suggest increased neural responding in key structures for the processing of both emotional and cognitive aspects of body-symptom information in PHA, reflecting potential neural correlates of a negative somatic symptom interpretation bias.

Keywords Pathological health anxiety · Implicit association test · Functional magnetic resonance imaging · Cognitive control · Emotional response

Introduction

Pathological health anxiety (PHA), formally termed hypochondriasis, is characterized by the conviction of suffering from a severe illness. It is assumed that in PHA, bodily sensations trigger worries about having a severe illness. However, whether this worrying process is mainly driven by an enhanced emotional response to body sensations or by the cognitive inability to disengage from them or by the interaction of both is still an open question.

The central feature of healthy anxiety is a preoccupation with the belief that one has, or is in danger of developing, a serious medical condition based on the misinterpretation of benign (or minor) bodily sensations [1]. PHA is highly common in primary care with a prevalence of 0.8–9.5% [2, 3]. While it is beyond doubt that PHA represents a serious challenge for the patients, as well as for the health care

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system, the diagnostic classification is still under debate [4, 5]. Thus, several classification approaches have been proposed. Among the different approaches, the so-called Fink criteria [6] have the advantage that they provide promising empirically based diagnostical criteria for PHA. In the combined cognitive bias hypothesis (CCBH), which is widely applied in anxiety and affective disorders, it is proposed that cognitive biases (of attention, memory, and interpretation) influence each other and interact to maintain a mental disorder [7]. In PHA, it is assumed that patients possess illness-related schemata in their memory that guide attention to illness-related cues, leading to misinterpretations of bodily sensations as risk of severe health threat [8, 9]. First evidence for this assumption came from studies on PHA using self-report questionnaires [10, 11]. Due to introspective limitations and response biases in explicit self-reports [12], it seems important to also apply implicit (experimental) tasks to investigate the biased processing of health-threat-related information in PHA.

The IAT [13] represents a widely used paradigm to explore automatic evaluative responses to critical stimuli and has been successfully applied in several mental disorders [14–16]. Reaction times (RT) are used to determine the relative strength of associations between concepts (e.g., illness versus neutral words) and attributes (e.g., dangerous versus harmless) based on the notion that faster processing (shorter RT) is associated with stronger associations, and incongruent pairings causing longer RT [13, 17].

According to dual-process models [18, 19], there are two modes of information processing: an implicit and an explicit mode. The implicit mode allows fast and preconscious information processing and the result can be perceived as an affective response to a stimulus. Conversely, the explicit mode is a conscious process that is guided by rule-based inferences, consuming individuals' cognitive recourses. In the IAT, the implicit and the explicit mode can be assumed to interact; i.e., more controlled cognitive effort is required to produce a correct response under incongruent conditions (reflecting the explicit mode) if there is a strong implicit bias (e.g., a strong automatic emotional response, reflecting the implicit mode). In the congruent condition, a correct response relies on automatic associations, probably leading to even faster responses with a more pronounced implicit bias (emphasizing the implicit mode) [17, 20]. Thus, in particular, the incongruent condition represents a joint effect of automatic (probably implicit) stimulus evaluations and cognitive control (probably explicit) processes in the IAT [20, 21].

To disentangle this joint effect, fMRI probably offers an efficient way for observing both activation reflecting automatic evaluation, as well as activation reflecting effortful mechanisms to inhibit implicitly biased response tendencies. The IAT was used in several studies on implicit associations (e.g., concerning gender and racial bias) that revealed activation mainly in amygdala and fronto-parietal network [22–25]. The amygdala is sensitive to salience [26] and ambiguity [27, 28], and is a key structure in the processing of threat-related stimuli [29, 30], thus reflecting neural mechanisms of initial automatic (implicit) stimulus evaluation [31, 32]. The fronto-parietal network, with the dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC, especially superior parietal cortex and inferior parietal lobes), plays a crucial role in cognitive control [33, 34], suggesting that activation in DLPFC and PPC during IAT reflects cognitive control for overcoming implicit biases [25, 35]. However, most research focusing on the neural basis of implicit associations used an indirect approach, applying regression analyses between IAT scores measured outside the scanner and neural activity from a separate task applied within the scanner [36].

Applying a direct approach, Mier et al. [37] recently used fMRI to investigate the neural correlates of implicit associations between body symptoms and the concept dangerous with an IAT in healthy participants who varied in the extent of health anxiety. Results of this body-symptom IAT showed both enhanced activation in DLPFC and PPC during incongruency and an association between the degree of health anxiety and incongruency-related activation in Nucleus accumbens (Nacc), DLPFC, and PCC. A drawback of this study was that participants fulfilling diagnostic criteria for PHA (i.e., hypochondriasis) were not included. Hence, the investigation of patients with PHA is pending. So far, only two fMRI studies included participants with PHA [38, 39]. Both studies applied an emotional Stroop task. In the study of van den Heuvel et al. [39], PHA patients had enhanced fronto-striatal involvement when processing obsessive–compulsive disorder-related and panic disorder-related words in comparison to a healthy control group. Although the results indicate that patients with PHA show increased cognitive elaboration for all disorder-related threats, the PHA group was considered as a clinical control group and no PHA-specific word material was used. Mier et al. [38] used PHA-specific word materials. The PHA group showed amygdala and rostral anterior cingulate hyperactivation in comparison to patients with depression and healthy controls, suggesting both an enhanced emotional reaction and a disability to cognitively disengage from potential health threats.

The aim of the present study was to investigate automatic evaluative processes of illness-related stimuli and its neural correlates in patients with PHA. For this purpose, we enrolled patients with PHA, a group of patients with depression, as well as a non-patient control group, and applied an fMRI adaption of a body-symptom IAT [37]. Since patients with PHA are characterized by high levels of negative affect and often present with comorbid depression [40], a group of patients with depression can help controlling

for the effect of negative affect on implicit processing. In addition, recent evidence demonstrated the validity of the CCBH for depression [41] by showing an interdependence of interpretation, memory, and attention in participants with subclinical depression. Furthermore, it was demonstrated that patients with depression are sensitive to a depression symptom IAT accompanied by aberrant activity in medial prefrontal cortex and DLPFC [35]. These results suggest that patients with depression represent an adequate clinical control group to investigate the specificity of an implicit bias for body-symptom words in PHA. We assumed stronger implicit associations between the concepts "symptom" and "dangerous" in the PHA group in comparison to both control groups in terms of reaction times. In terms of brain activation, we expected hyperactivity in amygdala and Nacc in response to the body-symptom words in the PHA group compared to the control groups, reflecting a stronger automatic emotional response. Based on our previous study with the IAT [37], we also expected to find neural correlates of enhanced cognitive control to inhibit implicitly biased response tendencies, as well as implicit stimulus evaluations; i.e., we hypothesized enhanced activation in DLPFC and PPC in the PHA group in comparison to both control groups.

Materials and methods

Participants

100 participants of a larger investigation of cognitive-emotional processing in PHA [40, 41] completed the IAT task. Four of them had to be excluded, three due to response accuracy below chance level and one due to low quality of the fMRI data. 96 participants, 32 participants with PHA, 29 with depression, and 35 healthy subjects were included in the final analyses. All participants were right-handed and had normal or corrected-to-normal vision. Groups were matched for age, gender, and education (see Table 1 for details). The study was approved by the Ethics Committee of the Medical Faculty Mannheim, University of Heidelberg, Germany and conducted in concordance with the declaration of Helsinki. Before participating in the study, participants were informed about the study procedure and purposes and provided written informed consent. Mental disorders were assessed with the Structured Interview for DSM-IV Axis I disorders (SCID-I) [42]. Patients were allowed to have comorbidities, except for schizophrenia and addiction. Under the comorbidities, the most prevalent was anxiety disorders with 65.6% of the PHA patients and 34.5% of the depressive controls having any anxiety disorder. 28.1% of participants in the PHA group had a current affective disorder (major depression, or dysthymia). Further comorbidities were under 10% with the highest prevalence of somatic symptom disorder (9.4% in the PHA group and 0% in the depressive control group). Additional items from the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) [43] were used for the interview-based diagnosis of PHA according to the diagnostic criteria introduced by Fink et al. [6]. The clinical interviews were conducted by six experienced clinical psychologists specially trained by an expert in SCID and SCAN. None of the participants of both control groups fulfilled diagnostic criteria for hypochondriasis according to the SCID-I, or the Fink interview. Regarding the PHA group, 65.6% had hypochondriasis according to the SCID-I, and 68.8% severe health anxiety and 31.2% mild health anxiety according to the Fink criteria. Participants completed the Whiteley Index, Patient Health Questionnaire Depression, and Patient Health Questionnaire Somatic to assess symptom characteristics and severity scores (see Table 1).

Questionnaires

The Whiteley Index (WI) is a widely used self-report questionnaire for the dimensional assessment of PHA that consists of 14 dichotomous items. A sum score of 8 or more points serves as a cut-off score for the detection of clinically relevant health anxiety [44]. Cronbach's α coefficient of the WI in former research was 0.73. Reliability, validity,

Table 1 Sample characteristics

	PHA	DEP	HC	F	χ^2 value	Post-hoc
Gender (% of female)	59	52	54	–	0.38	–
Education (% ≥ 12 years)	75	66	71	–	0.67	–
Age	40.28 ± 12.11	42.34 ± 12.54	41.63 ± 13.72	0.21	–	–
PHQ-9	9.38 ± 4.78	16.79 ± 4.32	1.86 ± 2.25	117.53***	–	DEP > PHA > HC
PHQ-15	11.34 ± 4.93	8.17 ± 4.76	2.14 ± 1.73	45.86***	–	DEP > PHA > HC
WI	10.47 ± 1.83	1.59 ± 1.32	0.91 ± 0.98	458.75***	–	PHA > DEP, HC

PHA pathological health anxiety group, *DEP* depression group, *HC* healthy control group, *PHQ-9* Patient Health Questionnaire Depression, *PHQ-15* Patient Health Questionnaire Somatic, *WI* Whiteley-Index

*** $p < 0.001$

and specificity for the measurement of PHA have also been demonstrated [45].

The Patient Health Questionnaire Depression (PHQ-9) is the 9-item depression module from the full PHQ. Each of the nine PHQ depression items corresponds to one of the DSM-IV Diagnostic Criteria for major depressive disorder [1]. The optimal cut-off score for detecting major depressive disorder is 10 [46].

The Patient Health Questionnaire Somatic (PHQ-15) assesses somatic symptom severity and is used as a screening instrument for somatoform disorders. Somatic symptom severity is reflected in a sum score of the 15 items (range 0–30 point), and classified as severe by scores from 15 to 30 [47].

The body-symptom implicit association task (body-symptom IAT)

The suitability of the fMRI-adapted body-symptom IAT has been demonstrated in a study on cognitive mechanisms of PHA in healthy subjects [37]. The body-symptom IAT involves two concept categories (ten body-symptom words and ten neural words) and two attribute categories (five harmless-related adjectives and five danger-related adjectives). In the concept categories, body-symptom words related to common bodily complaints or sensations (such as cough and sickness) that are potential triggers of illness concerns for patient with PHA, as well as neutral words related to household (such as basin and plate) were used (for details see Supplementary Table 6). The congruent condition required participants to sort body-symptom words and danger-related adjectives as a group, as well as household words and harmless adjectives as the other group; on the contrary, body-symptom words and harmless adjectives as a group, as well as household words and danger-related words as the other group in the incongruent condition. All participants started with the congruent condition. As control condition rows of lower case or capital letters were presented as target stimuli [24, 37]. Participants were required to sort the letter strings to the attributes “lower case” or “capital”. The experimental design is shown in Fig. 1.

The IAT started with a session of 12 blocks of the congruent condition, followed by a session of 12 blocks of the incongruent condition. Since a fixed order was used, the position of the control attributes on the screen was exchanged for the incongruent condition to account for possible differences in reversal learning abilities and related cognitive effort between participants. Both the congruent and the incongruent condition included six word and six letter blocks in alternating order. A fixation cross was presented between blocks for 13 s, followed by an instruction for the new block for 2 s. Within each block, 20 stimuli were presented with a fixed duration of 1.5 s, separated by a fixation cross of a mean duration of 300 ms. The total duration of each block, including intertrial interval, was around 50 s.

In the present study, responses were recorded with a Lumitiouch optical response device (Photon Control Inc Burnaby, BC, Canada). The task was implemented with the Presentation software, version 9.50 (Neurobehavioral Systems Albany, CA, USA). Stimuli were presented by VisuaStim video goggles (Resonance Technology Inc, Northridge, CA, USA). Prior to the IAT, participants completed an emotional Stroop task [38].

Image acquisition

The study was performed on a 3 Tesla Siemens Tim TRIO whole-body magnetic resonance imaging scanner (Siemens

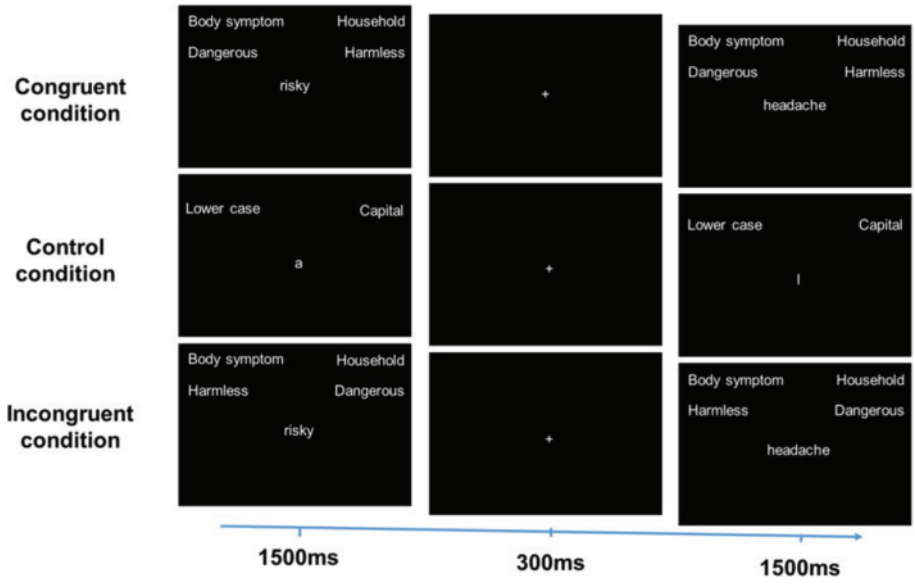

Fig. 1 Body-symptom word implicit association task

Medical Systems, Erlangen, Germany). Before functional imaging, a T1-weighted anatomical scan was acquired (162 slices, 1 × 1 × 1 mm voxel size). Functional scans were obtained using a $T2^*$-weighted gradient echo planar imaging sequence (TR = 2000 ms; TA = 100 ms; TE = 50 ms; flip angle 90 degree; field of view = 224 mm; 64 × 64 matrix). Each volume consisted of 28 slices, collected in a descending order with a slice-thickness of 3 mm with 1 mm gap (resulting voxel size: 3 × 3 × 4 mm). Each session (congruent and incongruent) contained 189 scans, with 378 scans for the whole experiment.

Data analyses

FMRI data analyses were accomplished with SPM8 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK). Data preprocessing included realignment, spatial normalization (MNI template) with resampling to a 3 × 3 × 3 mm voxel size, and spatially smoothing with an 8 mm FWHM kernel.

Preprocessed data were subjected to a fixed effect first-level analysis including both sessions. Repressors for each condition were defined and convolved with a box car function. To minimize the influence of movement-related variance, we included the six movement parameters of the realignment procedure as covariates of no interest. To investigate the effect of the word material, the main effect of the words was analyzed with the contrast: (incongruent words, congruent words) > (incongruent letters, congruent letters). To investigate the implicit associations, the interaction contrast that compares incongruent word blocks with congruent word blocks with reference to the control conditions was used: (incongruent words > incongruent letters) > (congruent words > congruent letters). Additional analyses within the sessions were conducted with the contrasts: incongruent condition (incongruent words > incongruent letters), as well as congruent condition (congruent words > congruent letters).

For second-level group analyses, we conducted one sample *t* tests across all participants to analyze the main effect of the word material, as well as of the implicit associations between body-symptom words and the attribute dangerous. The differences between groups for the word material, as well as for implicit associations were analyzed with regressions, assuming that patients with PHA have the highest activation, followed by patients with depression. Post-hoc comparisons between groups were achieved by applying two sample *t* tests. Differences between the two control groups can be found in the Supplementary Materials (Supplementary Table 5). The significance threshold for whole brain analyses was $p < 0.05$ FWE-corrected, $k = 5$. In addition, we applied region of interest analyses with the ROIs: DLPFC (BA 46 and BA 9), PPC (BA 7 and BA 40), and amygdala. These ROIs were taken from the WFU pickatlas. In addition, based on an anatomical atlas, a mask for the Nacc was used that has also been used in the previous body-symptom IAT [37]. Significance threshold for the ROI analyses was $p < 0.05$ small volume corrected (svc), $k = 5$. Furthermore, we conducted group comparisons with ROI analyses for the incongruent and the congruent condition separately. The findings can be found in the Supplementary Materials (Supplementary Tables 3 and 4).

Behavioral data were analyzed with SPSS version 22. According to Greenwald et al., the IAT effect was analyzed by the improved D-score algorithm (known as D_4, or IAT D_{600}) [48]. The D-score for the IAT is a quotient of the difference between the mean latency of the incongruent condition and of the congruent condition divided by the pooled standard deviation. Specifically for the IAT D_{600}, the pooled standard deviation (SD) is calculated only with latencies of correct responses across conditions. Furthermore, the latencies for each false response are replaced with the mean latency for correct responses of that condition and an error penalty (600 ms). The mean latencies for each condition are calculated separately. Higher scores reflect stronger implicit associations between the concept body symptoms and the attribute dangerous. The IAT D_{600} scores and the reaction times were subjected to ANOVAs. Paired *t* tests were used for post-hoc analyses if interaction effects were significant.

Results

Behavioral data

Analyses revealed larger D_{600} scores for words than for letters. Furthermore, words in comparison to letters, as well as the incongruent in comparison to the congruent categorization resulted in longer reaction times. However, no significant group differences were found. Mean response latencies, accuracies, and D_{600} scores across all participants, as well as for the three groups separately and their comparisons are presented in Supplementary Text and Supplementary Table 1.

Functional imaging data

Task effects across all participants

Word materials One sample *t* tests showed significantly enhanced activation for words compared to letters in bilateral middle temporal gyrus, bilateral posterior cingulate, bilateral cerebellum, right inferior frontal gyrus (IFG), right cuneus, left middle frontal gyrus, and left superior parietal lobe (see Table 2; Fig. 2a). In addition, ROI analyses revealed bilaterally enhanced activation in PPC and DLPFC.

Table 2 Activations in response to the word materials [(incongruent words, congruent words) > (incongruent letters, congruent letters)] across all participants

Area	BA	L/R	Cluster	MNI			*t* value	*p* value
				x	*y*	*z*		
Whole brain analyses								
Inferior frontal gyrus	47	R	5411	33	23	−2	15.09	<0.001
Claustrum		L		−30	20	1	13.55	<0.001
Middle frontal gyrus	46	L		−48	29	28	12.25	<0.001
Superior parietal lobe	7	L	2353	−30	−55	43	13.29	<0.001
Superior Parietal Lobe	7	L		−27	−67	43	12.60	<0.001
Precuneus	7	L		−12	−70	46	12.15	<0.001
Middle temporal gyrus	22	L	375	−54	−43	−2	9.18	<0.001
Middle temporal gyrus	20	L		−57	−43	−14	7.71	<0.001
Middle occipital gyrus	18	L	174	−24	−97	1	8.55	<0.001
Middle temporal gyrus	20	R	62	60	−43	−11	7.93	<0.001
Posterior cingulate	23	L	49	−6	−28	28	7.03	<0.001
Posterior cingulate	23	R		6	−28	28	5.19	0.01
Cuneus	30	R	28	3	−73	−7	6.25	<0.001
Cerebellum cluster								
Declive		L	854	−9	−76	−29	14.20	<0.001
Declive		R		9	−76	−29	12.44	<0.001
Culmen		L		−27	−61	−32	9.19	<0.001
Region of interest analyses								
Posterior parietal cortex	7, 40	L	948	−33	−58	46	12.66	<0.001
Posterior parietal cortex	7, 40	R	925	12	−37	49	11.86	<0.001
Dorsolateral prefrontal cortex	9, 46	R	398	45	44	22	11.08	<0.001
Dorsolateral prefrontal cortex	9, 46	L	375	−51	29	28	11.99	<0.001

Significance threshold for whole brain analyses is set to $p < 0.05$ FWE-corrected, $k = 5$, and for the ROI analyses to $p < 0.05$ svc, $k = 5$, subcluster peaks are inserted

Implicit bias The incongruent versus congruent words condition (see Table 3; Fig. 2b) showed significantly increased activation in bilateral superior parietal lobe, bilateral middle frontal gyrus, bilateral cerebellum, bilateral thalamus, right insula, left inferior temporal gyrus, left middle occipital gyrus, and left middle temporal gyrus. ROI analyses revealed bilaterally enhanced activation in the PPC and DLPFC during the incongruent in comparison to the congruent condition.

Group effects

Word materials Whole brain analysis with a regression for group comparison (PHA > depression > healthy controls, see Table 4) for words versus letters revealed no significant group differences. ROI analyses, however, showed significantly enhanced activation in bilateral amygdala (Fig. 3), right PPC, as well as a trend for higher activation in the PHA group in left Nacc.

Post-hoc two sample *t* tests revealed no significant differences between groups, when applying whole brain analyses. ROI analyses, however, revealed that patients with PHA showed hyperactivation in bilateral amygdala and right PPC as well as in left Nacc at a trend level in comparison to the healthy subjects. However, there was no significant difference between the two patient groups (Table 5).

Implicit bias Whole brain analysis with a regression for group differences (PHA > depression > healthy controls, see Table 6) in implicit associations revealed no significant group differences, but ROI analyses revealed significantly higher activation in bilateral PPC (Fig. 4), and in left DLPFC at a trend level.

Again, post-hoc two sample tests revealed no differences between groups, when applying whole brain analyses. ROI analyses, however, showed that patients with PHA had significantly enhanced activation in left PCC and at a trend level in right PPC and left Nacc in comparison to the healthy control group. ROI analyses revealed no significant differences between the two patient groups (Table 7).

Discussion

The present study aimed at investigating the neural basis of the negative automatic interpretation bias of body symptoms

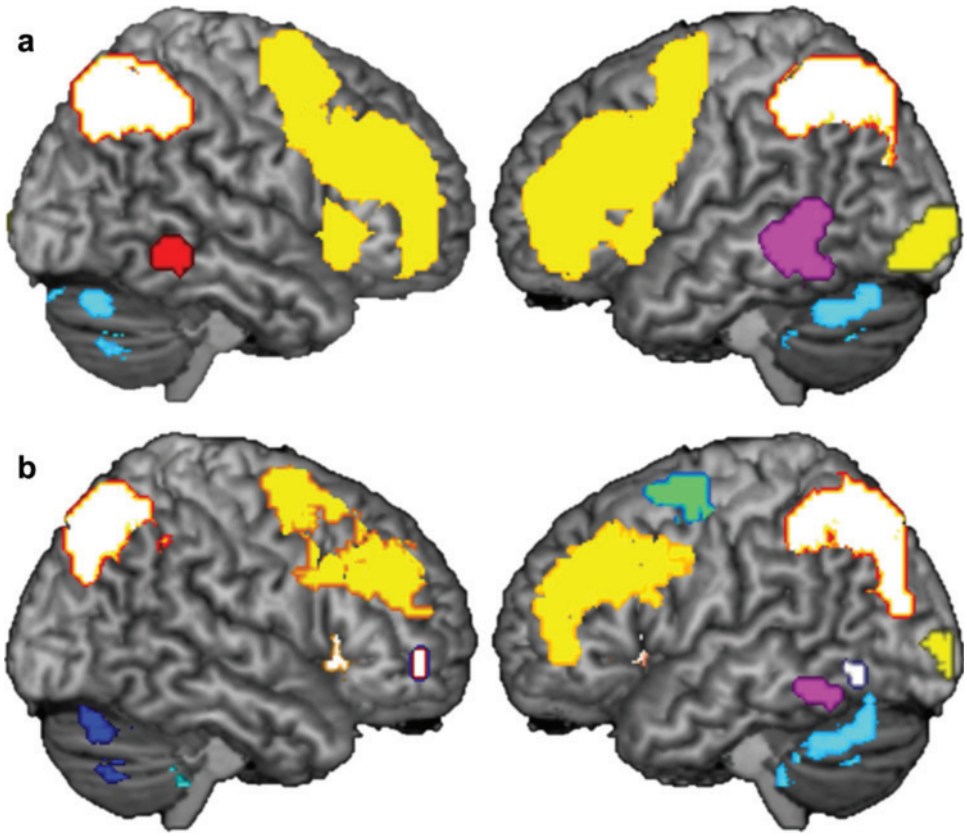

Fig. 2 Condition effects across all participants. **a** Higher activation for word than letter processing (words > letters). **b** Enhanced activation in the incongruent condition in comparison to the congruent condition [(incongruent words > incongruent letters) > (congruent words > congruent letters)]. Activation differences are displayed with a significance threshold of $p < 0.05$ FWE-corrected, $k = 10$

that represents a central feature of PHA. To investigate the specificity of this bias in patients suffering from PHA, two control groups, i.e., healthy participants and patients fulfilling diagnostic criteria for a depressive disorder, were included. In general, patients with PHA showed aberrant processing of body-symptom words in the IAT on the neural but not on the behavioral level. The findings elucidate aberrant neural activation patterns in patients with PHA compared to clinical as well as non-clinical comparison groups and contribute to the growing knowledge on biased information processing in PHA [9].

Behavioral results showed that across all participants, word materials attracted more attention than letters and that the association between the concepts "body symptoms" and "dangerous" was stronger than the association between "body symptoms" and "harmless". For the word materials in comparison to the letters, we found increased activation in IFG, and structures associated with fronto-parietal network (FPN, including DLPFC and PPC). The IFG plays a crucial role in response inhibition [49] and is closely linked to executive control [50]. The PPC is related to proprioception [51], attentional processing [52], working memory [53] and various cognitive functions, including attention, and action processing [54, 55]. The DLPFC is highly correlated with working-memory processes [56]. The FPN in general is linked to cognitive control and working memory [57, 58], and is involved in top–down control of visual attention [34]. Taken together, these results indicate that word material attracted subjects' visual attention and executive functions more than letters as used in the control condition of the IAT. Regarding the implicit association effect, we found increased activation in the FPN. Thus, the incongruent condition in comparison to the congruent condition resulted in a stronger involvement of an executive network, most likely due to the necessity to inhibit pre-potent responses, suggesting the suitability of our task to assess the neural correlates of implicit associations.

In contrast to our hypothesis, group comparisons revealed no evidence of a significantly stronger bias in patients with PHA on the behavioral level (neither in the raw RTs nor in case of the D_{600} score). However, regarding brain activation, hyperactivation in bilateral amygdala, right PPC, and on a trend level in left Nacc was found in response to the word stimuli in the PHA group in comparison to both control groups. The amygdala is a key structure in the processing of threat-related stimuli in terms of rapid pre-attentive detection of threat-related stimuli and in the processing of emotional stimuli [59]. As a part of the FPN, the PPC is not only involved in visuospatial processing [60], but also related to attention processes [61], as well as cognitive control [34]. The hyperactivation in right PPC is in line with the lateralization theory proposing the

Table 3 Activation during the assessment of implicit body-symptom associations [(incongruent words > incongruent letters) > (congruent words > congruent letters)] across all participants

Area	BA	L/R	Cluster	MNI			*t* value	*p* value
				x	*y*	*z*		
Whole brain analyses								
Superior parietal lobe	7	L	2004	−12	−70	55	9.39	<0.001
Precuneus	19	L		−27	−67	40	9.27	<0.001
Superior parietal lobe	7	R		15	−67	58	7.62	<0.001
Middle frontal gyrus	10	R	880	42	47	31	8.35	<0.001
Middle frontal gyrus	6	R		30	−1	64	7.73	<0.001
Middle frontal gyrus	9	R		57	23	31	7.12	<0.001
Middle frontal gyrus	46	L	583	−45	38	31	8.40	<0.001
Middle frontal gyrus	9	L		−54	20	31	7.33	<0.001
Inferior frontal gyrus	6	L		−42	−1	34	6.93	<0.001
Middle frontal gyrus	6	L	219	−30	−1	64	7.12	<0.001
Superior frontal gyrus	6	L		−24	5	58	6.40	<0.001
Middle frontal gyrus	6	L		−27	−1	49	6.03	0.001
Insula	13	R	92	33	20	7	6.14	<0.001
Claustrum		L	77	−27	20	1	7.03	<0.001
Inferior temporal gyrus	20	L	54	−54	−16	−14	8.08	<0.001
Middle occipital gyrus	18	L	28	−24	−97	4	6.05	0.001
Lingual gyrus	18	L		−12	−100	−8	4.97	0.030
Middle frontal gyrus	11	R	26	33	50	−8	5.44	0.005
Middle temporal gyrus	37	L	17	−45	−64	−5	5.46	0.005
Lentiform nucleus		R	16	15	−7	1	5.19	0.014
Thalamus		R		9	−13	1	5.10	0.019
Thalamus		L	9	9	−19	4	5.02	0.025
Thalamus		L		12	−10	1	5.02	0.025
Cerebellum clusters								
Declive		L	227	−36	−67	−29	6.65	<0.001
Tuber		L		−33	−58	−38	6.42	<0.001
Cerebellar tonsil		L		−24	−43	−47	5.98	0.001
Declive		L	191	−6	−76	−26	6.79	<0.001
Declive		R		9	−79	−26	6.32	<0.001
Uvula		R	140	30	−64	−32	6.85	<0.001
Inferior semi-lunar lobe		R		39	−67	−47	5.72	0.002
Cerebellar tonsil		R	21	18	−46	−50	5.51	0.004
Cerebellar tonsil		R		27	−43	−47	5.07	0.021
Region of interest analyses								
Posterior parietal cortex	7, 40	R	1501	15	−67	58	7.62	<0.001
Posterior parietal cortex	7, 40	L	1329	−12	−70	55	9.39	<0.001
Dorsolateral prefrontal cortex	9, 46	R	506	42	44	34	8.35	<0.001
Dorsolateral prefrontal cortex	9, 46	L	455	−45	38	31	8.40	<0.001

Significance threshold for whole brain analyses is $p < 0.05$ FWE-corrected, $k = 5$, and for the ROI analyses to $p < 0.05$ svc, $k = 5$, subcluster peaks are inserted

right hemisphere to be mainly involved in the processing of negative affective information [62]. It is assumed that stimulation of projections from the amygdala to the ventral striatum interrupts goal-directed processes in favor of responding to unexpected threats [63]. Furthermore, the Nacc is linked to emotional arousal, salience processing, as well as behavioral or self-related stimuli [64, 65]. Hyperactivation of left Nacc in PHA might be explained, in contrast to assumptions of the lateralization theory, by an animal study showing that especially left Nacc responds to negative stimuli [66]. Taken together, these findings most likely indicate that the word stimuli were more salient for the PHA group compared to the control groups and resulted in a stronger emotional response.

Table 4 Group comparisons (pathological health anxiety group > depression group > healthy control group) of brain activation in response to the word materials [(incongruent words, congruent words) > (incongruent letters, congruent letters)]

Area	BA	L/R	Cluster	MNI			*t* value	*p* value
				x	*y*	*z*		
Whole brain analyses								
None								
Region of interest analyses								
Posterior parietal cortex	7, 40	R	93	18	−67	64	3.90	0.04
Nucleus accumbens		L	61	−12	17	−5	2.89	0.06^{+}
Amygdala		L	17	−21	−4	−26	3.03	0.02
Amygdala		R	14	21	−7	−23	2.74	0.04

Significance threshold for whole brain analyses is set to $p < 0.05$ FWE-corrected, $k = 5$, and for the ROI analyses to $p < 0.05$ svc, $k = 5$, trends are indicated by $^{+}$

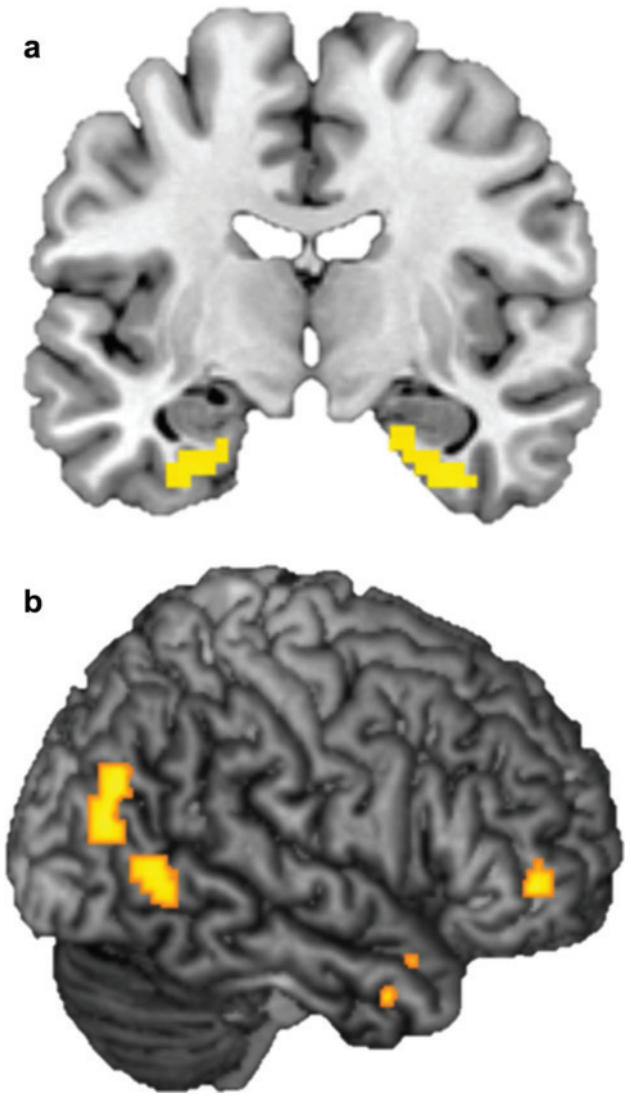

Fig. 3 Hyperactivation in the pathological health anxiety group for the word materials (words > letters) in comparison to both control groups. **a** Hyperactivation in the amygdala. **b** Hyperactivation in PPC. Activation differences are displayed with a significance threshold of $p < 0.001$, $k = 10$

Regarding an implicit bias in terms of more negative body-symptom evaluations in PHA group, inconsistent with Witthöft et al. [9], we found no significant group differences in RTs. The present sample is a subsample of the study by Witthöft et al. [9] and might lack the power to reveal the group differences in response times ($N = 96$ in the fMRI study and $N = 192$ in the behavioral study). However, with respect to the neural mechanism of implicit body-symptom associations, in consistence with Mier et al. [37], the PHA group showed hyperactivation in the PPC, namely, in superior parietal lobe (BA 7) and inferior parietal lobe (BA 40). Moreover, the PHA group showed a trend for hyperactivation in the left DLPFC. As mentioned above, the PPC and DLPFC play crucial roles in the FPN [34]. This hyperactivation might indicate that patients with PHA required more controlled cognitive efforts to show a correct response under the incongruent condition, compared to the control groups. Patients in the PHA group in comparison to the healthy controls had hyperactivation in bilateral PPC and left Nacc. This might suggest that PHA patients had both stronger emotional response, and higher need for recruitment of cognitive control and executive functions. In light of dual-process models [19], these results suggest enhanced processing of the word stimuli both within the implicit and explicit mode in PHA.

In a nutshell, we found evidence for aberrant processing in patients with PHA (a) emotionally, as reflected in increased activation in amygdala and Nacc that are linked to salience and processing of threat-related stimuli and (b) cognitively, as reflected in increased activation in DLPFC and PPC which are linked to cognitive control and executive functions.

Limitation

This study did not conduct explicit measures of attitudes toward body symptoms and was thus unable to explore corresponding neural correlates. Future symptom-relevant fMRI studies in PHA might prefer to combine explicit and

Table 5 Post-hoc two sample *t* tests for group differences in brain activation in response to the word materials [(incongruent words, congruent words) > (incongruent letters, congruent letters)]

Area	BA	L/R	Cluster	MNI			*t* value	*p* value
				x	*y*	*z*		
PHA > HC								
Whole brain analyses								
None								
Region of interest analyses								
Posterior parietal cortex	7, 40	R	92	18	−67	64	3.99	0.04
Nucleus accumbens		L	75	−15	20	−2	2.84	0.07^{+}
Amygdala		L	17	−21	−4	−26	3.12	0.02
Amygdala		R	13	21	−7	−23	2.73	0.05
PHA > DEP								
Whole brain analyses								
None								
Region of interest analyses								
None								

Significance threshold for whole brain analyses is $p < 0.5$ FWE-corrected, $k = 5$, and for the ROI analyses is $p < 0.05$ svc, $k = 5$, trends are indicated by $^{+}$

PHA pathological health anxiety group, *DEP* depression group, *HC* healthy control group

Table 6 Group comparisons (PHA > depression > healthy controls) of brain activations during the assessment of implicit body-symptom associations [(incongruent words > incongruent letters) > (congruent words > congruent letters)]

Area	BA	L/R	Cluster	MNI			*t* value	*p* value
				x	y	z		
Whole brain analyses								
None								
Region of interest analyses								
Posterior parietal cortex	7, 40	L	1080	−63	−34	40	3.98	0.03
Posterior parietal cortex	7, 40	R	920	60	−28	28	4.24	0.01
Dorsolateral prefrontal cortex	9, 46	L	115	−48	44	16	3.46	0.06^{+}

Significance threshold for whole brain analyses is $p < 0.5$ FWE-corrected, $k = 5$, and for the ROI analyses is $p < 0.05$ svc, $k = 5$, trends are indicated by $^{+}$

implicit attitude measures to figure out their potential associations. Furthermore, consistent with most former research [24, 25], the findings of this study are based on a block design that combines the categorization of the target words (i.e., body-symptom words) with the categorization of non-target words (i.e., household words). Thus, the results reflect a mixed effect of both trial types. Future studies may use an event-related design to figure out the specificity of the target trials [23]. The present study did not find (a) group differences in reaction times from incongruent as well as congruent condition and (b) group differences between the two clinical groups in the regions of interest. It might be due to the drawbacks of the IAT which is highly related to the order of the paring of concepts and attributes and in particular to personal experience. Furthermore, it has been criticized to be susceptible to conscious control [67]. Thus, future studies may develop new methods or algorithms to investigate biased processing of health-threat-related materials in PHA. Post-hoc comparisons between PHA patients and depressive patients were not significant. Thus, our findings might not be specific for PHA, but aberrations in brain activation seem to be more pronounced in patients with PHA than in patients with a depressive disorder. However, a substantial number of PHA patients had comorbidities, especially anxiety disorders and depressive disorders. These comorbidities may attenuate group differences with regard to the depressive control group. Future studies may aim at investigating PHA patients without any comorbidities. Furthermore, future studies applying patients with anxiety disorders (e.g., with panic disorder) as clinical control group would help shedding light on the specificity of the aberrations in brain activation for PHA under the anxiety disorders.

Conclusions

Taken together, we found patients with PHA having increased activation in amygdala and Nacc when processing

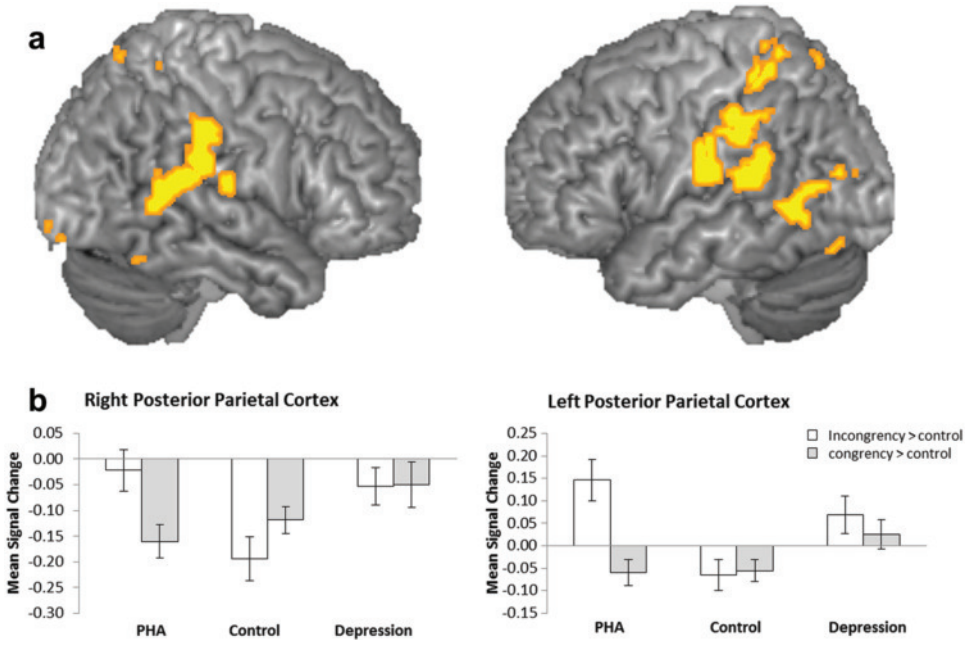

Fig. 4 Hyperactivation in the pathological health anxiety group during incongruency processing. **a** Enhanced activation in the incongruent condition in comparison to the congruent condition [(incongruent words > incongruent letters) > (congruent words > congruent letters)] in pathological health anxiety in comparison to both control groups. Activation differences are displayed with a significance threshold of $p < 0.001$, $k = 10$. **b** Activation differences between incongruent words and incongruent letters, and congruent words and congruent letters in the left and right posterior parietal cortex. Displayed is the mean signal change in PPC activation for the three groups. *PHA* pathological health anxiety group, *Control* healthy control group, *Depression* depressive control group

Table 7 Post-hoc two sample *t* tests for group differences in activation during the assessment of implicit body-symptom associations [(incongruent words > incongruent letters) > (congruent words > congruent letters)]

Area	BA	L/R	Cluster	MNI			*t* value	*p* value
				x	*y*	*z*		
PHA > HC								
Whole brain analyses								
None								
Region of interest analyses								
Posterior parietal cortex	7, 40	L	944	−63	−34	40	3.80	0.03
Posterior parietal cortex	7, 40	R	865	63	−31	28	3.92	0.05
Nucleus accumbens		L	31	−18	17	−2	2.74	0.09^{+}
PHA > DEP								
Whole brain analyses								
None								
Region of interest analyses								
None								

Significance threshold for whole brain analyses is $p < 0.5$ FWE-corrected, $k = 5$, and for the ROI analyses is $p < 0.05$ svc, $k = 5$, trends are indicated by $^{+}$

PHA pathological health anxiety group, *DEP* depression group, *HC* healthy control group

body-symptom-related words, probably indicating a strong emotional reaction and an implicit evaluation bias. Furthermore, hyperactivation in the DLPFC and PPC was revealed in PHA during the incongruent condition compared to the congruent condition, probably demonstrating higher cognitive effort to overcome the body-symptom related implicit bias. It is important to stress that behavioral indicators of the IAT seem less suited to map characteristic cognitive biases in PHA. The neural findings, however, are in line with the combined cognitive bias hypothesis (CCBH) [7] that has recently been applied to the realm of PHA [9], suggesting that attentional and evaluative biases might maintain

the symptoms of PHA. Currently, exposure and re-attribution based psychotherapeutic treatments (e.g., Kerstner et al. [41]) seem to be most promising in targeting the cognitive biases in PHA. Longitudinal fMRI studies are needed to test whether the observed abnormalities change as a function of successful therapeutic interventions.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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