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Neural processing of emotional facial stimuli in specific phobia: An fMRI study

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Abstract

Background: Patients with specific phobia (SP) show altered brain activation when confronted with phobia-specific stimuli. It is unclear whether this pathogenic activation pattern generalizes to other emotional stimuli. This study addresses this question by employing a well-powered sample while implementing an established paradigm using nonspecific aversive facial stimuli.

Methods: $N = 111$ patients with SP, spider subtype, and $N = 111$ healthy controls (HCs) performed a supraliminal emotional face-matching paradigm contrasting aversive faces versus shapes in a 3-T magnetic resonance imaging scanner. We performed region of interest (ROI) analyses for the amygdala, the insula, and the anterior cingulate cortex using univariate as well as machine-learning-based multivariate statistics based on this data. Additionally, we investigated functional connectivity by means of psychophysiological interaction (PPI).

Results: Although the presentation of emotional faces showed significant activation in all three ROIs across both groups, no group differences emerged in all ROIs. Across both groups and in the HC > SP contrast, PPI analyses showed significant task-related connectivity of brain areas typically linked to higher-order emotion processing with the amygdala. The machine learning approach based on whole-brain activity patterns could significantly differentiate the groups with 73% balanced accuracy.

Conclusions: Patients suffering from SP are characterized by differences in the connectivity of the amygdala and areas typically linked to emotional processing in response to aversive facial stimuli (inferior parietal cortex, fusiform gyrus, middle

cingulate, postcentral cortex, and insula). This might implicate a subtle difference in the processing of nonspecific emotional stimuli and warrants more research furthering our understanding of neurofunctional alteration in patients with SP.

KEYWORDS
brain imaging/neuroimaging, functional MRI, neuroimaging, phobia/phobic disorders

1 | INTRODUCTION

Specific phobia (SP) is among the most prevalent mental disorders with an estimated 12-month prevalence of 6.4% and 22.7 million affected people in Europe (Wittchen et al., 2011) and a high burden of disease (Kessler et al., 2012). The underlying neurofunctional alterations are not yet well understood (Stefanescu et al., 2018). A deeper understanding of these mechanisms could significantly broaden our knowledge of the development of the disorder and thus help in the improvement of treating it. The existing literature implies changed neurofunctional activity in several key brain areas in patients with SP during the confrontation with fear-inducing phobia-specific stimuli (Del Casale et al., 2012; Etkin & Wager, 2007).

Most of these studies examine SP patients while exposed to phobia-specific stimuli, yielding consistent results of heightened neurofunctional activity in the amygdala as well as the insula and the anterior cingulate cortex (ACC) compared to healthy controls (Dilger et al., 2003; Fredrikson & Furmark, 2006; Goossens et al., 2007; Peñate et al., 2017; Siegel et al., 2017; Straube, Glauer, et al., 2006; Straube, Mentzel, et al., 2006). For two current meta-analyses, see Gentili et al. (2019), who stress the importance of whole-brain analyses in addition to regions of interest (ROI) analyses, and Chavanne and Robinson (2021), who corroborate the importance of the insula and the cingulate gyrus.

It is not yet clear if heightened neurofunctional activity generalizes to nonspecific aversive stimuli. This could shed light on the specificity of these neurofunctional alterations (Wright et al., 2003) and have implications for clinical practice, as it would mean that exposure to stimuli other than the feared one is necessary to treat patients with SP. When comparing patients with SP (animal phobia) to HC, previous studies found heightened neurofunctional activity in the amygdala, insula, putamen, and middle temporal gyrus when exposed to fear-inducing images like shark or knife attacks (Schienle et al., 2005), and in the rostral ACC in an emotional counting Stroop paradigm, but lower amygdala and insula activation as well as heightened functional connectivity between the left amygdala and the rostral ACC (Britton et al., 2009). Finally, Schaefer et al. (2014) found a higher neurofunctional activity of the amygdala in patients with SP (snake phobia) compared to HC during the exposure to generally fear-inducing video clips, while Killgore et al. (2014) found a decreased activation of the ventromedial prefrontal cortex (vmPFC) when being confronted with masked emotional faces.

However, multiple other studies did not find activation differences between patients with SP (spider phobia) and HC in response to nonspecific aversive stimuli, specifically fear-inducing scenes (Schienle et al., 2007), mutilations, and animal attacks (Sabatinelli et al., 2005; Schweckendiek et al., 2011; Wendt et al., 2008): Furthermore, Wright et al. (2003) found no heightened neurological processing of emotionally valenced human faces in patients with small animal phobia compared to HC.

These conflicting findings might result from several methodological issues. First, all studies mentioned above examined comparably small groups of participants, typically less than 30 patients. Second, the utilized paradigms and stimuli were heterogeneous, further complicating a comparison between different studies. Third, inclusion criteria for phobic individuals were heterogeneous, ranging from subclinical self-reported phobic symptoms to a clinical diagnosis of SP.

Hence, we wanted to examine whether a well-powered sample of properly diagnosed SP patients (spider phobia) with minimal comorbidities shows altered neurofunctional activity in response to aversive face stimuli compared to HC. As stimuli, we used angry and fearful faces (Hariri et al., 2002), that have been shown to be aversive to different groups of participants, both with and without mental disorders (Dannlowski et al., 2012; Nikolova et al., 2014; Redlich et al., 2015; Schneider et al., 2018). Furthermore, we investigated whether functional connectivity patterns of the amygdala differentiate between patients with SP and HC, as this region (and its connectivity to other brain areas) has been frequently shown to be of critical importance to the disorder (Lai, 2020; Stefanescu et al., 2018).

On the basis of these studies, we hypothesized (1) that aversive faces robustly activate the amygdala, the insula, and the ACC, compared to neutral stimuli (in our case, geometric shapes) across both study groups (main effect of task); (2) that this activation is higher in the SP group than in the HC group. Furthermore, we assumed (3) that we can also differentiate the two groups with a machine learning (ML) approach, which has not yet been done. Finally, based on the works of Britton and colleagues (2009) we hypothesized (4) that the functional connectivity of the amygdala and (because of results regarding hypothesis 2; see Section 3.3) the calcarine gyrus is altered in the SP group.

2 | METHOD

The SP group was part of a subproject of a Transregional Collaborative Research Center (CRC-TRR58 "Fear, Anxiety, Anxiety Disorders"). Complete information on the methods and goals of this

project can be found elsewhere (Schwarzmeier et al., 2019). The control group was acquired in parallel within the Marburg-Münster Affective Disorders Cohort Study (MACS; Kircher et al., 2019; Vogelbacher et al., 2018) using the identical magnetic resonance imaging (MRI) setup. All data is available upon request from the corresponding author. This analysis is a secondary analysis of a subsample of these two studies.

2.1 | Participants

$N = 270$ participants responded to public notices and online advertisements for a spider phobia study and were invited following a short telephone interview. Inclusion criteria comprised a clinically significant SP, assessed with the structured clinical interview for DSM-IV (SCID; Wittchen et al., 1997; $n = 123$ exclusions), as well as adherence to other criteria like the ability to participate in the MRI procedure ($n = 7$ exclusions), minimal movement in the MRI (less than 3.3 mm of total movement or 3.3° of total rotation; $n = 5$ exclusions) and having no other comorbid mental diagnosis except for mild or moderate depressive episodes (also assessed with the SCID) and other SP from the animal subtype ($n = 13$ exclusions). $N = 11$ participants dropped out between measurement points. For full inclusion criteria, see Schwarzmeier et al. (2019). From the initial sample, $n = 111$ participants fulfilled these criteria. In this study, we only used the Münster Cohort of this bicentric study to ensure comparability with the HC group. For the HC group ($n = 111$), participants had to adhere to the same inclusion criteria as the SP group, except the diagnosis of SP. Out of the MACS sample, the HC group was chosen by matching the SP group for sex and age. Demographic and clinical characteristics can be found in Table 1. According to a power analysis using g*power 3.1.9.2 (Faul et al., 2007) our sample size resulted in sufficient power (1-beta=80%) to detect effect sizes as low as Cohen's $d = 0.33$ at $\alpha = .05$ (family-wise error [FWE]-corrected for the search volume).

2.2 | Procedure

Participants were first invited for a diagnostic interview in which inclusion was secured and the SCID interview as well as the questionnaires were conducted. For the SP sample, one of these questionnaires was the Spider Phobia Questionnaire (SPQ; Hamm, 2017; Klorman et al., 1974) to measure the severity of spider phobia. It consists of 31 binary items. In our sample, Cronbach's α was .75. We included participants for the SP group with a sum score of 20 or higher. Additionally, we conducted the behavioral avoidance test (BAT) with a bird spider (Grammostola Rosea) in a plastic box in the SP sample. In a second appointment, the MRI examination was conducted. The study protocols were reviewed by the Ethics Committee of the Medical Faculty at Muenster University and are in accordance with the Declaration of Helsinki. Written informed consent was obtained.

TABLE 1 Study sample characteristics by diagnosis groups

		SP	HC	
	N	mean (SD)	mean (SD)	p value
Demographics				
Sex (f/m)	222	97/14	97/14	1
Age	222	27.8 (8.74)	29.01 (8.55)	.299
Years of education	222	14.61 (2.82)	14.36 (2.65)	.493
Comorbid diagnoses	222	6	0	<.001
Depressive disorder	222	3	0	<.001
Second SP	222	3	0	<.001
Questionnaire measures				
SPQ	111	22.59 (2.03)	-	-
STAI-T	222	34.59 (7.67)	34.57 (8.67)	.98

Note: A χ^2-test was used to test for significance of group differences regarding sex and Multivariate Analysis of Variance (MAnoVa) was used to test for significance of group differences in other variables. None of the depressive disorders was more severe than a moderate depressive disorder; all the comorbid specific phobias were of the animal subtype, where the spider phobia was predominant.
Abbreviations: f, female; HC, healthy control; m, male; SP, specific phobia; SPQ, Spider Phobia Questionnaire; STAI-T, State-Trait Anxiety Inventory, Trait Subtest.

2.3 | fMRI data acquisition

All participants were examined in a 3-T Siemens Prisma MRI. Functional images were collected with a T2* weighted echo-planar imaging (EPI) sequence sensitive to blood oxygenation level-dependent (BOLD) contrast in ascending order (matrix = 64 × 64, slices = 33, FOV = 210, voxel size = 3.3 × 3.3 × 3.8 mm, 10% slice gap, TE = 29ms, TR = 2.0 s, flip angle = 90°). Slices covered the whole brain and were positioned along the anterior–posterior commissure line with a tilted angle of 20°. Stimuli were presented via a back-projection monitor using Presentation 20 (Neurobehavioral Systems; www.neurobs.de).

We used a paradigm originally developed by Hariri et al. (2002) that has been used extensively in our research group and by others (Dannlowski et al., 2011, 2012, 2016; Domschke et al., 2012; Nikolova et al., 2014; Redlich, Grotegerd, et al., 2015; Redlich, Stacey, et al., 2015; Redlich et al., 2019; Schneider et al., 2018). The paradigm consists of four blocks of negative faces (either angry or fearful, each block lasting 47 s) from the Ekman and Friesen (1976) stimulus set and five blocks of a sensorimotor control task (circles and ellipses). Participants had to choose which of two pictures (either faces or shapes) displayed in the bottom row is identical to a picture displayed above. Each block consisted of six faces or shapes trios, shown for four seconds and with a variable interstimulus interval of 2–6 s. Each block lasted 35 s and the task lasted 363 s. All included participants had a success rate of 89% or higher, there was no difference between the two groups in terms of success, $t(220)= -1.372$; $p = .171$.

2.4 | Statistical analysis

Data were preprocessed using statistical parametric mapping software (SPM8, Wellcome Department of Cognitive Neurology, www.fil.ion.ucl.ac.uk/spm). In preprocessing, images were realigned using a set of six rigid-body transformations determined for each image, unwarped, and normalized to the Montreal Neurological Institute International Consortium for Brain Mapping (MNI) template. Lastly, images were smoothed with a 6 mm full-width at half-maximum (FWHM) Gaussian kernel.

2.4.1 | First-level analysis

We modeled the onsets and durations of the two experimental conditions (faces and shapes) using a canonical hemodynamic response function in the context of the general linear model. We corrected this model for serial correlations and applied a high-pass filter of 128 s to reduce low-frequency noise. We finally generated one contrast image per subject, contrasting the faces condition with the shapes baseline.

2.4.2 | Second-level analysis

The following calculations were performed within SPM12, first whole brain (with a minimum cluster size of $k = 10$) and then for our three ROIs: the bilateral amygdala ($k = 462$), insula ($k = 3627$), and ACC ($k = 2712$), three regions having shown to be central in the neurofunctionality of anxiety (Wager, 2012). These three ROIs were obtained using the Wake Forest PickAtlas (Maldjian et al., 2003) which follows the AAL atlas (Rolls et al., 2020; Tzourio-Mazoyer et al., 2002) definitions. We corrected for multiple testing with the FWE-method and a significance voxel threshold of $p_{FWE} < .05$ and repeated these analyses with a more lenient threshold of $p_{unc} < .05$.

As proof of general activation as expected, we analyzed activation for the contrast image faces>shapes, regardless of group (hypothesis 1). Subsequently, we conducted one ANOVA with group as a between-subjects factor to test for group differences (hypothesis 2). If this group contrast yielded significant results, we conducted post-hoc directed t tests (SP > HC and HC > SP).

2.4.3 | Machine learning approach

In addition to standard univariate analyses, we employed a multivariate machine learning (ML) approach to differentiate the two groups using identical data (faces > shapes contrast, once whole brain and once with the amygdala, insula and ACC ROI; hypothesis 3). We used the PHOTON toolbox developed in our workgroup (Leenings et al., 2020; see https://www.photon-ai.com).

To get a non-biased performance estimation, we applied a nested cross-validation scheme. This scheme consisted of 10 inner validation loops to optimize hyperparameters of the ML model and ten outer validation loops to estimate model performance, as proposed by Poldrack et al. (2020).

For the whole-brain analysis, all voxels within a whole-brain mask with a resolution of 4x4x4 mm were used. For the ROI analysis, we used all voxels within the three ROIs as input to the machine learning analysis. For detailed information, see Supporting Information A.

2.4.4 | PPI analysis

To examine connectivity patterns of the amygdala based on our task (hypothesis 4), we conducted a psychophysiological interaction (PPI) analysis (Friston et al., 1997; Gitelman et al., 2003). We extracted the time series of both amygdalae and of the significant cluster of the calcarine gyrus (see Section 3.3) for every subject as the physiological factor. The shapes versus faces contrast (see Section 2.4.1 first-level analysis) served as the psychological factor. The resulting contrast images of the PPI term were then entered into a second-level analysis, first over all participants and second with group as a between-group effect.

3 | RESULTS

3.1 | Effect of task: Faces versus shapes

As expected, we found significantly stronger activation in the faces condition compared to the shapes condition in all three of our ROIs: In the amygdala (left: $k = 143$, peak voxel: $x = -20$, $y = -4$, $z = -20$; $t(220) = 14.02$, $p_{FWE} < .001$; right: $k = 171$, peak voxel: $x = 22$, $y = -4$, $z = -18$; $t(220) = 13.48$; $p_{FWE} < .001$;), the insula (left: $k = 21$, peak voxel: $x = -36$, $y = -14$, $z = 22$; $t(220) = 4.75$; $p_{FWE} = .002$; right: $k = 71$, peak voxel: $x = 36$, $y = -14$, $z = 18$; $t(220) = 5.97$, $p_{FWE} < .001$) and the ACC (left: $k = 2$, peak voxel: $x = -6$, $y = 0$, $z = 30$; $t(220) = 4.29$; $p_{FWE} = .009$ and right: $k = 1$, peak voxel: $x = -6$, $y = 4$, $z = 28$; $t(220) = 4.17$; $p_{FWE} = .014$; right: $k = 4$, peak voxel: $x = 8$, $y = 6$, $z = 28$; $t(220) = 5.85$; $p_{FWE} < .001$). See Table 2 for the whole-brain results.

3.2 | Group comparison: SP>HC

When contrasting SP > HC, the whole-brain analysis of the faces>shapes contrast yielded no significant above-threshold results. Furthermore, none of the ROIs showed significant activation differences, both when applying a significance threshold of $p_{FWE} < .05$ and even when applying an uncorrected threshold of $p_{unc} < .05$.

3.3 | Group comparison: HC > SP

When comparing HC > SP, the whole-brain analysis showed significant activation differences in the occipital lobe, specifically in the right calcarine gyrus ($k = 56$; peak voxel: $x = 8$, $y = -92$, $z = -4$; $t(220)$

	MNI coordinates			p_{FWE} value	k
	x	y	z		
Temporal and occipital cluster, including:					
L Precuneus	22	−98	−8	<.001	14,776
L Precentral gyrus					
R Fusiform gyrus					
L Frontal inferior orbital gyrus					
L Occipital middle gyrus					
L Amygdala					
R Amygdala					
R Frontal gyrus, including:					
R Inferior orbital frontal ggyrus	42	18	24	<.001	1273
R Inferior frontal triangular gyrus					
R Middle frontal gyrus					
R Inferior frontal opercular gyrus					
Frontal inferior medial cluster, including:					
R Gyrus rectus	2	46	−18	<.001	407
R Medial frontal orbital gyrus					
L Gyrus rectus					
R Frontal orbital gyrus, including:					
R Frontal inferior orbital gyrus	30	34	−18	<.001	295
R Frontal superior orbital gyrus					
R Frontal middle orbital gyrus					
R Temporal gyrus	52	−34	4	<.001	372
L Cerebellum	−10	−82	−38	<.001	163
L Temporal gyrus	−58	−4	−24	<.001	533
L Caudate nucleus	−8	20	12	<.001	142
L Frontal superior gyrus	−12	36	58	<.001	17
	−12	58	36	<.001	37
L Frontal middle gyrus	−40	18	54	<.001	55
R Precentral gyrus	44	−20	66	<.001	10
R Temporal cluster, including					
R Temporal superior gyrus	46	−62	22	<.001	160
R Angular gyrus					
R Precuneus					
R Precuneus	24	−54	10	<.001	53
R Calcarine fissure					
R Precuneus	4	−62	34	<.001	147
R Cerebellum crus	16	−84	−38	<.001	61
R ACC	8	4	26	<.001	53
L + R Frontal superior gyrus	4	60	38	<.001	61

TABLE 2   Results of the faces>shapes contrast across both groups, sorted by statistical significance

	MNI coordinates			p_{FWE} value	k
	x	y	z		
R Temporal pole gyrus	40	18	−40	<.001	45
R Postcentral gyrus	46	−10	42	<.001	75
L Precuneus	−22	−60	10	<.001	34
L ACC	−12	−34	56	<.001	22
R Frontal middle gyrus	38	24	54	<.001	12
R Insula	36	−14	18	<.001	48
L Postcentral gyrus	−40	−12	38	.001	23
L Angular gyrus	−36	−52	28	.003	12

Notes: In the case that a cluster included more than five areas, only areas with a size >3% of the cluster are reported (except for the amygdala because of its importance for this article).
Abbreviations: ACC, anterior cingulate cortex; L, left; R, right.

=5.57; p_{FWE} = .003). Again, none of the ROIs showed significant activation differences.

We are confident that the lack of univariate difference is not a result of type II errors due to insufficient statistical power. Our paradigm elicited strong reactions in brain regions thought to play key roles in the processing of fear and anxiety, namely the amygdala, the insula, and the ACC. Furthermore, even lowering the statistical threshold for the amygdala ROI to an overly lenient value of 0.05, uncorrected (resulting in a corrected α of .37, according to a Monte-Carlo simulation by means of the REST toolbox) still yielded no significant results in the selected contrast (SP > HC).

3.4 | Machine learning analysis approach

The ML analyses were able to classify our participants to their respective groups with above-chance balanced accuracies of 73% for the whole-brain analysis and 59% for the ROI analysis (p < .001 and p = .015, respectively). For more detailed results, see Tables S1 and S2.

3.5 | Psychophysiological interaction

Regarding the psychophysiological connectivity of the left amygdala across both groups, several areas (an occipital cluster including the fusiform gyrus, hippocampus, inferior frontal gyrus, insula, inferior parietal lobus, and calcarine lobus) showed significant results, see Table 3. When contrasting SP > HC, no significant connectivity differences could be found. Contrasting HC > SP, a few regions showed significant connectivity differences: the inferior parietal cortex, the fusiform gyrus, the middle cingulate cortex, the postcentral cortex, and the insula (see Table 3, Figure 1). HC showed a stronger increase of amygdala connectivity while processing faces versus shapes with these regions, hence a tighter coupling, compared to patients with SP.

The results of the PPI for the right amygdala and the calcarine gyrus across both groups were similar to the ones of the amygdala (see Tables 4 and 5). There were no significant connectivity differences in the group contrasts.

4 | DISCUSSION

The present study addressed the question of whether patients with specific phobia show altered activation when confronted with non-specific aversive stimuli, in our case emotional faces. Our results are threefold: First, we could not find any activation differences between a large group of patients with SP and an HC group except for a heightened activity of the calcarine gyrus in the HC group. Second, a multivariate machine learning approach could discriminate the two groups based on our contrast images significantly above chance level. Third, several areas of the brain like the middle cingulate cortex and the inferior parietal cortex displayed significant connectivity with the left amygdala in response to the faces > shapes contrast across both groups and the HC group showed significantly greater connectivity with the inferior parietal cortex, the insula, and the fusiform cortex.

4.1 | Activity and connectivity of the amygdala and the calcarine gyrus

The central role of the amygdala in processing fear is well documented (Adolphs, 2013; Davis, 1992; Panksepp et al., 2011; Tovote et al., 2015). Patients with SP show heightened activation when confronted with phobia-specific stimuli (Dilger et al., 2003). Our results show a strong reaction of the amygdala to our paradigm across both groups but no differences between the groups. This could be due to a ceiling effect in our data or indicate that the amygdala of patients with SP does not show heightened responsiveness to nonspecific emotional facial stimuli.

	MNI coordinates			P_{FWE} value	k
	x	y	z		
Across both groups					
Occipital cluster, including:					
R Middle occipital cortex	40	−50	−20	<.001	11982
L Inferior occipital cortex					
L Superior parietal gyrus					
R Fusiform gyrus					
R Inferior occipital cortex					
L Fusiform gyrus					
R Hippocampus	22	−28	−4	<.001	119
L Hippocampus	−18	−30	−2	<.001	111
R Gyrus frontalis inferior, pars Triangularis	50	18	26	<.001	616
L + R Insula	−38	−2	12	<.001	31
L Parietal inferior lobus	−54	−26	54	<.001	41
	−26	−52	48	.002	63
L Calcarine lobus	−18	−72	8	<.001	112
L Amygdala	−18	−6	−16	.001	24
L Gyrus frontalis inferior, pars Opercularis	−42	8	30	.002	32
R Cerebellum	16	−66	−44	.003	15
Temporal gyrus, including:					
R Middle temporal gyrus	50	−40	8	.007	19
R Superior temporal gyrus					
L Cerebellum	−24	−70	−50	.014	5
L Putamen	−32	−14	−4	.023	1
R Parahippocampal gyrus	18	−2	−22	.027	3
R Middle frontal gyrus	52	10	48	.035	1
L Precentral gyrus	−40	−18	64	.044	2
L Lingual gyrus	−4	−70	6	.044	1
Vermis cerebelli	4	−78	−30	.048	1
SP > HC					
No voxels over significance threshold					
HC > SP					
L Inferior parietal lobus	−42	−18	52	<.001	321
L Insula	−38	−2	14	.002	8
L Postcentral cortex	−44	−20	22	.010	13
L Inferior parietal lobus	−58	−18	44	.012	17
R Fusiform gyrus	28	−76	−8	.013	6
L ACC	−10	−24	48	.042	1

TABLE 3 Results of the connectivity (PPI) analysis of the left amygdala, showing an increase of connectivity in response to faces > shapes

Abbreviations: ACC, anterior cingulate cortex; HC, healthy controls; L, left; PPI, psychophysiological interaction; R, right; SP, spider phobia.

FIGURE 1 Activity difference and PPI results of the HC versus SP contrast. (a) Results of the faces>shapes contrast across both groups ($x = -32$, $y = 13$, $z = -5$). b) Results of the faces>shapes contrast in the HC > SP contrast ($x = 9$, $y = -89$, $z = -5$). c) Results of the PPI analysis (faces > shapes, left amygdala as seed region) across both groups ($x = 28$, $y = -28$, $z = 24$). d) Results of the PPI analysis (faces > shapes, left amygdala as seed region) in the HC > SP contrast ($x = -40$, $y = -12$, $z = 8$). In the coronal and the sagittal view, the significant parietal inferior cortex is shown. Additionally, the sagittal view shows the insula. In the axial view, the fusiform gyrus is shown. Color bar shows t values. Significance threshold: FWE, $p < .05$.
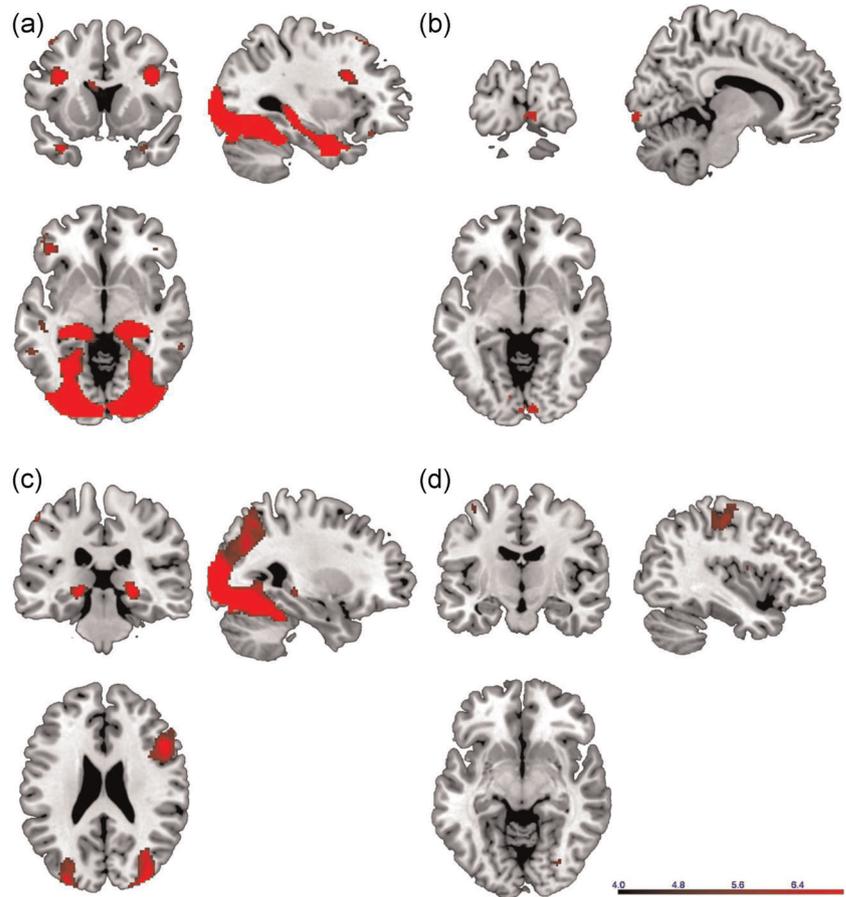
Regarding the PPI results across both groups, several areas showed a significant psychophysiological interaction with the amygdala. These results emphasize the importance of the amygdala in the processing of aversive stimuli and particularly emotional faces. All three utilized seed regions showed very similar psychophysiological interactions, potentially because of their high interconnectivity. Additionally, while we did not find areas of significantly higher connectivity with the left amygdala in SP compared to HC, we did find significant differences between the HC > SP contrast in clusters known to be active in the processing of emotional faces (Kropf et al., 2019; Radua et al., 2010): Both posterior parietal areas and the insula have been proposed to be part of a more complex, conscious processing of compared to a more direct, less elaborated route (Dbiec & LeDoux, 2009; LeDoux, 1996). In our study, HC participants did not show higher activation of these areas, but a stronger connection with the amygdala.

These results match those by studies showing a hypoconnectivity between the amygdala and a wide number of other brain areas in patients with anxiety disorders (Stefanescu et al., 2018; Xu et al., 2019). This altered connectivity could also be a neurofunctional basis of attentional bias and attentional control alterations found in patients with anxiety disorders (Kim et al., 2018; McNally, 2019; Shi et al., 2019), and could explain why SP patients have shown to have problems directing their attention away from perceived threats in other studies (Elsesser et al., 2006; Siev et al., 2020).

4.2 | Activity of the insula, ACC, and other brain areas

Similarly, our results regarding the insula and the ACC fit into the broader context of current research: Although both regions have been found to play a central role in the processing of anxiety and fear (Etkin & Wager, 2007; Goossens et al., 2007; Straube, Glauer, et al., 2006), our results and those of other studies (Sabatinelli et al., 2005; Schienle et al., 2007; Schienle et al., 2013; Schweckendiek et al., 2011; Wendt et al., 2008; Wright et al., 2003) seem to indicate that these differences in activation of the insula and the ACC in patients with SP cannot be seen in the processing of nonspecific aversive stimuli—except for the already discussed altered connectivity with the amygdala.

In addition, we found a hypoactivation of the calcarine gyrus in the SP group compared to HC in the faces>shapes contrast. Contradicting this, other researchers found a hyperactivation of the occipital lobe, and specifically the calcarine gyrus, in the same comparison (Van Strien & Van der Peijl, 2018; Wiemer & Pauli, 2016) which was suggested to be a transdiagnostic trait of heightened processing of threatening stimuli (Feldker et al., 2017). These divergent results could be explained by the nature of our stimuli: maybe patients with SP only show this hyperactivation when confronted with more fear-inducing or phobia-specific stimuli.

	MNI coordinates			P_{FWE} value	k
	x	y	z		
Across both groups					
Occipital cluster, including:					
L Inferior occipital cortex	38	−56	−180	<.001	9858
R Middle temporal cortex					
R Middle occipital cortex					
R Fusiform gyrus					
L Fusiform gyrus					
R Inferior occipital cortex					
L + R Cerebellum crus					
L + R Cerebellum					
L Superior occipital cortex					
L Calcarine sulcus					
R Lingual gyrus					
Lingual cluster, including:					
R Lingual gyrus	24	−28	−4	<.001	132
	22	−64	6	.001	104
R Hippocampus					
R Thalamus					
R Calcarine sulcus					
Lingual cluster, including:					
L Lingual gyrus	−18	−30	−2	<.001	103
L Hippocampus					
L Thalamus					
R Gyrus frontalis inferior, pars Triangularis	50	18	26	<.001	174
	48	34	12	.003	68
Right amygdala cluster, including:					
R Amygdala	18	−2	−22	<.001	22
R Parahippocampal gyrus					
R Hippocampus					
Left amygdala cluster, including					
L Amygdala	−22	−2	−22	.002	19
L Hippocampus					
L Cerebellum	−20	−70	50	.005	22
L + R Calcarine sulcus	4	−82	6	.021	8
Vermis cerebelli	0	−76	−16	.028	2
R Angular gyrus	32	−56	40	.030	7
R Parietal inferior lobus					
R Cerebellum	18	−66	−46	.043	2
L Cerebellum	−28	−62	−32	.048	1

TABLE 4 Results of the connectivity (PPI) analysis of the right amygdala, showing an increase of connectivity in response to faces > shapes

	MNI coordinates			P_{FWE} value	k
	x	y	z		
SP > HC					
No voxels over significance threshold					
HC > SP					
No voxels over significance threshold					

Abbreviations: ACC, anterior cingulate cortex; HC, healthy controls; L, left; PPI, psychophysiological interaction; R, right; SP, spider phobia.

TABLE 5 Results of the connectivity (PPI) analysis of the calcarine sulcus, showing an increase of connectivity in response to faces > shapes

	MNI coordinates			P_{FWE} value	k
	x	y	z		
Across both groups					
Occipital cluster, including:					
R Middle temporal cortex	−22	−90	−14	<.001	5857
R Middle occipital cortex					
L + R Fusiform gyrus					
L + R Inferior occipital cortex					
L Occipital superior cortex					
L Cerebellum crus					
R Lingual gyrus					
R Hippocampus	22	−28	−2	<.001	25
R Thalamus					
L Hippocampus	−20	−30	−2	<.001	11
L Thalamus					
L Precentral gyrus	−36	−14	68	.001	5
L Precentral gyrus	−38	−20	68	.002	2
R Cerebellum	14	−88	−18	.003	1
Central cluster, including:					
L Postcentral gyrus	−44	−22	64	.004	10
L Precentral gyrus					
R Caudate	18	28	−6	.006	13
L Precentral gyrus	−42	−26	66	.009	1
Amygdala cluster, including:					
L Amygdala	−20	−4	−24	.013	5
L Hippocampus					
L Postcentral gyrus	−52	−18	56	.021	1
R Frontal middle gyrus	50	10	50	.030	2
L Precentral gyrus	−42	−16	64	.033	1
R Parahippocampal gyrus	18	−2	−24	.038	1
SP > HC					
No voxels over significance threshold					
HC > SP					
No voxels over significance threshold					

Abbreviations: HC, healthy controls; L, left; PPI, psychophysiological interaction; R, right; SP, spider phobia.

4.3 | Machine learning results

Our ML results show a discrimination success of over chance, which is similar or slightly less successful than comparable approaches that tried to discriminate between SP and HC on the basis of structural MRI data (Lueken et al., 2015) or to predict therapy outcome in patients with several different mental diseases (Ball et al., 2014; Frick et al., 2020; Hahn et al., 2015; Hilbert et al., 2020; Leehr et al., 2021; Månsson et al., 2015). We find that our ML paradigm utilizing activity in the whole brain is more successful than one limiting itself to our ROIs, once again corroborating our theory that differences in neurofunctional activity of patients with SP are not limited to these areas. Although these results are promising, their clinical relevance still must be verified. This might be due to the poor discriminative power of the underlying data in our study. However, another potential explanation could be that earlier studies had comparably small sample sizes, which might have led to overfitting of the data (Flint et al., 2019) and thus replication with larger samples is needed (Rashid & Calhoun, 2020).

4.4 | Limitations

Some limitations of the presented study should be mentioned. First, emotional faces may not be best suited to examine the reaction of patients with SP to nonspecific aversive stimuli. Almost all studies that are in line with our results used paradigms utilizing emotionally valenced but not graphic stimuli, commonly pictures of faces (Wright et al., 2003), while studies that found differences used more graphic stimuli (Sabatinelli et al., 2005; Schienle et al., 2005; Schweckendiek et al., 2011; Wendt et al., 2008). Additionally, the Hariri paradigm has not been used in a study with SP before. Thus, we are not able to offer a fully satisfying solution to the heterogeneity problem in our field of research. Another potential critique on the Hariri paradigm could be that it is in fact too successful, resulting in a ceiling effect that prevents the SP group from showing even higher activation than the HC group. Furthermore, the difference in activation in the calcarine gyrus could also be explained by a hypoactivation to shapes in the HC group. As our paradigm did not include a baseline condition, we cannot rule this out.

Finally, we cannot generalize our data to all subtypes of SP, as our sample only consisted of patients with spider phobia. Studies have shown that there are neurofunctional differences especially between patients with animal phobia and dental phobia (Lueken et al., 2011, 2014, 2015; Stefanescu et al., 2018). Second, our sample size consisted primarily of female participants (87%, see Table 1), which is not unusual (Britton et al., 2009; Schienle et al., 2005; Wendt et al., 2008), but limits the generalizability to male patients suffering from SP.

4.5 | Conclusion

Although we could find strong neurofunctional differences in our paradigm across both groups, SP patients' activity did only differ from HC's in the calcarine gyrus in a univariate approach. However, we did find altered task-related connectivity between the amygdala and regions typically associated with more elaborated processing of emotional stimuli. Together with the ability to differentiate the two groups above chance in a multivariate ML approach based on our paradigm, these results might point to a small difference in processing nonspecific aversive stimuli that do not show themselves when processing emotional faces but might potentially be found in other paradigms using phobia-specific or different aversive nonspecific stimuli. Some methodological questions need further research, mainly whether the nature of the stimuli plays a role in differentiating the neurofunctional reactions to nonspecific aversive stimuli of patients with SP from those without.

CONFLICT OF INTERESTS
The authors declare that thee are no conflict of interests.

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The data is available upon reasonable request from the corresponding author.

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