Cortical and Subcortical Brain Alterations in Specific Phobia and Its Animal and Blood-Injection-Injury Subtypes: A Mega-Analysis From the ENIGMA Anxiety Working Group

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Objective: Specific phobia is a common anxiety disorder, but the literature on associated brain structure alterations exhibits substantial gaps. The ENIGMA Anxiety Working Group examined brain structure differences between individuals with specific phobias and healthy control subjects as well as between the animal and blood-injection-injury (BII) subtypes of specific phobia. Additionally, the authors investigated associations of brain structure with symptom severity and age (youths vs. adults).

Methods: Data sets from 31 original studies were combined to create a final sample with 1,452 participants with phobia and 2,991 healthy participants (62.7% female; ages 5–90). Imaging processing and quality control were performed using established ENIGMA protocols. Subcortical volumes as well as cortical surface area and thickness were examined in a preregistered analysis.

Results: Compared with the healthy control group, the phobia group showed mostly smaller subcortical volumes, mixed surface differences, and larger cortical thickness across a substantial number of regions. The phobia subgroups also showed differences, including, as hypothesized, larger medial orbitofrontal cortex thickness in BII phobia (N=182) compared with animal phobia (N=739). All findings were driven by adult participants; no significant results were observed in children and adolescents.

Conclusions: Brain alterations associated with specific phobia exceeded those of other anxiety disorders in comparable analyses in extent and effect size and were not limited to reductions in brain structure. Moreover, phenomenological differences between phobia subgroups were reflected in diverging neural underpinnings, including brain areas related to fear processing and higher cognitive processes. The findings implicate brain structure alterations in specific phobia, although subcortical alterations in particular may also relate to broader internalizing psychopathology.

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Specific phobia is the most prevalent anxiety disorder (1, 2), with global lifetime prevalence ranging between 2.6% and 12.5% (3). According to DSM-IV-TR and DSM-5, it involves marked and disproportionate fear and anxiety or frequent avoidance of particular objects or situations. Its onset is often early in childhood (3), and many cases develop into internalizing disorders (4). Given its prototypical fear reaction and early onset, specific phobia has been used as a model disorder to investigate the neural processing of fear and fear circuitry dysfunctions (5, 6). Functional neuroimaging studies of the disorder implicate the anterior to mid-cingulate gyrus, the amygdala, the insula, the thalamus, and the inferior frontal gyrus (7, 8). These alterations have been related to the rapid processing of external threat stimuli (thalamus [5]), stimulus saliency (amygdala [5]; particularly interoception: insula [7]; particularly exteroception: anterior cingulate cortex [ACC] [7]), fear conditioning (amygdala [5]), emotion regulation (ACC [5]), and impaired emotion appraisal (inferior frontal gyrus [8]). The present study complements these functional correlates by reporting findings from a large multisite investigation examining neuroanatomical correlates of specific phobia.

In contrast to functional MRI investigations, few studies have examined differences in brain structure associated with specific phobia, and those were generally conducted in small samples and targeted isolated regions of interest (e.g., 9–11). Moreover, while some areas seemed to emerge as relevant, the direction of observed differences was mixed. Because structural alterations may underlie the disorder-related functional differences, deeper knowledge of structural correlates is needed. The literature possesses three major gaps. First, the animal phobia subtype exhibits a prototypical, sympathetically mediated fear response (12), whereas the blood-injection-injury (BII) subtype shows a less clear-cut response, with some evidence of a unique diphasic fear response (13, 14). The corresponding neural activation patterns seem to implicate fear-related components, such as the amygdala, insula, dorsal ACC, and thalamus in the animal subtype, but are less clear-cut in the BII subtype (15–17). In contrast, the orbitofrontal cortex (OFC) has been implicated in BII phobia (15, 17). Given the paucity of research on brain structure associated with specific phobia, it remains unclear whether these subtypes indeed manifest unique neurostructural correlates corresponding to functional activation patterns.

The few available preliminary findings indicate that this might only be partially the case, particularly for the ACC being associated with specific phobia in general and the OFC being associated with the BII subtype specifically (18, 19). Second, despite the early onset of specific phobia during childhood, few studies have examined brain structure related to specific phobia before adulthood. Third, previous research on anxiety disorders demonstrated that depressive comorbidity was associated with altered gray matter volumes (20). However, it is unclear whether comorbid depressive symptoms are also related to the altered brain structure associated with specific phobia.

Our aim in this investigation was to address these gaps by comparing brain structure in individuals with specific phobia and healthy individuals. Within the Enhancing Neuroimaging Genetics Through Meta-Analysis (ENIGMA) collaboration (21), the ENIGMA Anxiety Working Group (22) obtained 33 data sets with information on neurostructural correlates of specific phobia and its animal and BII subtypes, of which 31 data sets (age range, 5–90 years) were included. As there was no substantial basis of structural research in specific phobia on which we could formulate directed hypotheses, we examined the following hypotheses: 1) Compared with healthy control subjects, individuals with specific phobia, across all subtypes, would show altered cortical thickness and surface area in the dorsal ACC and the insula, and altered subcortical volumes in the amygdala and thalamus. Additionally, 2) individuals with animal phobia would show altered amygdala and thalamus volumes when compared with healthy control subjects or individuals with BII phobia, while those with BII phobia would show altered cortical thickness and surface area in OFC areas when compared with healthy control subjects or individuals with animal phobia. Furthermore, we expected 3) a linear association of these metrics with symptom severity and 4) a linear association with depression severity for insula, dorsal ACC, and amygdala metrics, both within the specific phobia group. This work is also the first investigation of brain structure associated with specific phobia in children and adolescents, but given the paucity of available studies, we refrained from formulating a hypothesis on the relationship with age.

METHODS

Samples

We collected 33 original data sets acquired on 43 distinct MRI scanners. We included only data sets with at least 10 subjects with specific phobia, leading to the inclusion of 31 of the collected data sets. Subjects were included who had current or past specific phobia, whether or not specific phobia was the primary diagnosis. Past studies used different criteria for determining specific phobia, from formal diagnoses using standardized clinical interviews to diagnostics based on established cutoff scores in questionnaires. We included both types of studies in order to maximize sample size. Subjects were excluded for a current or lifetime diagnosis of bipolar disorder, psychosis, or schizophrenia. No current or past diagnoses of any mental disorder were allowed for healthy control subjects. All participants provided written informed consent when participating in the original studies, and these original studies obtained approval from institutional review boards and ethics committees. This study was preregistered at the Open Science Framework (osf.io/n6bhz).

This project depended on data sets from original studies. Most of these original studies have not been analyzed for neurostructural correlates of specific phobia, with some

exceptions (18, 19, 23, 24). The present analysis provides unprecedented statistical power and heterogeneity regarding the number of participants with specific phobia included.

Imaging Processing and Quality Control

Original studies contributed their data to our mega-analysis either by processing their data on-site and sending the resulting subject-level data plus demographic and clinical variables or by sending us raw brain imaging data (structural T_1-weighted MR images) so that we performed the processing centrally. In both cases, imaging processing and quality control were performed using FreeSurfer (25) with established ENIGMA protocols and instructions for quality control (available at https://enigma.ini.usc.edu/protocols/imaging-protocols/). In short, structural images were segmented and processed to calculate volume data for eight subcortical regions per hemisphere and to calculate surface area and cortical thickness data for 34 cortical regions per hemisphere and total intracranial volume. Cortical region segmentation was performed according to the Desikan-Killiany cortical atlas (26). The resulting segmentations were checked visually for substantial over- or underestimation; this process was supported by summary statistics, box plots, and outlier histograms. Individuals were excluded from the cortical or subcortical analysis, respectively, if the FreeSurfer segmentation failed altogether, and if there were over- or underestimations in at least 25% of the cortical or subcortical regions. Otherwise, only the data from the affected regions were excluded.

Statistical Analysis

FreeSurfer-derived data for cortical and subcortical regions were used as input in a linear mixed model in R, version 4.0.4, including disorder state (specific phobia, healthy control subjects) as variable of interest and age, sex, and intracranial volume as fixed factors and scanner as random intercept (see Table S1 in the online supplement for an overview of scanner characteristics and procedures for grouping subjects across studies for this covariate). Here, we deviated from the preregistered analysis, as the model was overparameterized for many brain regions in the fundamental group comparison, and we thus reduced model complexity by eliminating random slopes. There were rare instances where models for individual areas were still overparameterized for phobia subtype comparisons and dimensional analyses, where we further reduced model complexity. This affected only nonsignificant areas. To limit multiple testing against the background of the large number of regions, we averaged left and right side cortical thickness, surface area, and subcortical volumes. Additionally, p values from all regions were corrected using the false discovery rate (FDR) as proposed by Benjamini and Hochberg (27), with FDR corrections run separately for subcortical volumes (eight regions), cortical surface area (34 regions), and cortical thickness (34 regions), in line with previous ENIGMA studies. Standard errors and effect sizes were calculated as described by Nakagawa and Cuthill (28).

A second preregistered analysis was performed to test for structural correlates specifically for the subtypes (hypothesis 2). This approach was limited to individuals with the animal and BII subtypes (including dental phobia) for whom sufficient data for subtype analysis were available (BII, N=182; animal, N=739; see Figure S1 in the online supplement). For the subtype analysis, disorder subtype (animal subtype, BII subtype) was used as variable of interest on specific phobia subjects only. Here, we included only individuals with specific phobia who had a single subtype, not those with multiple subtypes. As this analysis yielded interesting results, we conducted two additional post hoc analyses, with individuals with animal phobia versus healthy control subjects and individuals with BII phobia versus healthy control subjects, which were not included in the preregistered analysis.

Three further preregistered analyses examined dimensional associations by using phobia severity, trait anxiety, and depression severity as variables of interest (hypotheses 3 and 4). Because phobia severity was assessed using a broad range of questionnaires across original studies, we classified participants into 10 ordinal categories according to their questionnaire score within their original study. These 10 ordinal categories were used in linear mixed models (deviating from the preregistered analysis, which mistakenly specified ordinal regressions that would require ordinal outcomes rather than ordinal predictors). For trait anxiety and depression severity, we used scores on the State-Trait Anxiety Inventory–Trait version (29) and the Beck Depression Inventory–II (30), respectively.

Along with these main analyses, we conducted further exploratory analyses on the robustness of the results by testing whether areas still showed significant differences between groups when using only individuals with specific phobia with formal diagnoses, using only individuals with current specific phobia, using only individuals with specific phobia and healthy control subjects with and without medication, examining only adults (age >21 years) and only children and adolescents (≤21 years; in line with previous ENIGMA studies), excluding subjects from scanners with fewer than 10 participants, excluding subjects with additional comorbidities, and examining the impact of education, re-including outliers, and unilateral versus bilateral regions (for details, see the supplemental methods section in the online supplement). Given the diverging findings for the age groups in the analyses of adults only and children and adolescents only, we added further exploratory analyses on an age-by-diagnosis interaction (see the online supplement).

RESULTS

We received data for 5,330 individuals. Table 1 provides detailed information on the numbers of and reasons for excluded subjects. The final sample consisted of 4,443 participants, of whom 1,452 had specific phobia and 2,991 were healthy control subjects. Sociodemographic information is

TABLE 1. Number of initial images, number of included images, and reasons for exclusion, by site, in a mega-analysis of brain alterations in specific phobia[a]

	Initial Data Sets				FreeSurfer Fail	
Study	Cortical	Subcortical	Covariates	Complete	Cortical	Subcortical
Barcelona	52	52	52	**52**	0	0
BHRCS	605	605	2,511	**596**	0	0
BION-SP	29	29	29	**29**	0	0
Bochum	18	18	18	**18**	1	2
COMIC	12	12	12	**12**	0	0
Czuwaj	46	46	48	**46**	0	0
Dresden CRC940C5	187	187	182	**182**	2	0
Dresden phobia subtypes	95	95	126	**95**	0	0
Graz	86	86	86	**86**	0	1
Graz II	72	72	72	**72**	0	0
Greifswald	44	44	45	**44**	0	0
Jena	29	29	30	**29**	0	0
Marburg FOR2107 MR	532	532	532	**532**	0	0
Münster dental	38	38	38	**38**	0	0
Münster FOR2107 MS	275	275	275	**275**	0	0
Münster SFBTRR-58 C09	96	96	215	**96**	0	1
Münster spider	507	507	507	**507**	3	1
PHOBIA EXPOSURE	20	20	20	**20**	1	1
PNC	945	854	854	**717**	4	5
Protect-AD	57	57	57	**57**	1	0
RepSpi	38	38	38	**38**	0	0
SDAN	119	119	119	**119**	0	0
SHIP	995	977	995	**977**	80	0
SMARTSCAN	93	93	95	**93**	0	0
SPIN	14	14	14	**14**[c]	0	2
SPIN NF	19	19	19	**19**	11	11
Teneriffa	77	77	78	**77**	0	0
Uppsala	47	47	47	**47**	0	0
Vanderbilt	19	19	18	**18**	0	0
Würzburg SFBTRR-58 C09	87	87	87	**87**	0	0
Würzburg spider	36	36	36	**36**	4	5
Würzburg spider II	25	25	25	**25**	2	1
Würzburg spider III	16	16	0	**0**	0	0
Total	**5,330**	**5,221**	**7,280**	**5,053**	**109**	**28**

[a] For the initial data sets of cortical, subcortical, or covariate files, data sets (subjects) were counted regardless of whether raw MRI data or the results of the FreeSurfer preprocessing done on site were contributed. BHRCS=Brazilian High Risk Cohort Study; BION-SP=Bender Institute of Neuroimaging; COMIC=COMIC Research/Leeds and York Partnership NHS Foundation Trust; Dresden CRC940C5=German Research Foundation (DFG) Collaborative Research Center 940, project C5; Marburg FOR2107 MR=DFG Research Group 2107, Marburg site; Münster FOR2107 MS=DFG Research Group 2107, Münster site; Münster SFBTRR-58 C09=DFG Collaborative Research Center Transregio 58, project C09, Münster site; PNC=Philadelphia Neurodevelopmental Cohort; Protect-AD=Providing Tools for Effective Care and Treatment of Anxiety Disorders consortium, specific phobia sample; SDAN=Section on Development and Affective Neuroscience; SHIP=Study of Health in Pomerania; Würzburg SFBTRR-58 C09=DFG Collaborative Research Center Transregio 58, project C09, Würzburg site.
[b] Includes a group of individuals with social phobia without specific phobia who were thus not included in any group here.
[c] Not considered further because <10 initial specific phobia data sets were available.

provided in Table 2, and Table S2 in the online supplement lists current and lifetime comorbidities among the specific phobia samples. A comparison of sociodemographic variables found that individuals with specific phobia were more frequently female, were significantly younger, and had significantly fewer years of education compared with healthy control subjects (all p values <0.001).

Specific Phobia Participants Versus Healthy Control Subjects

The main group comparison showed significantly smaller subcortical volumes for the specific phobia group (N=1,452) compared with the healthy control group (N=2,991) in several regions, including the caudate, putamen, and hippocampus, significantly greater thickness in several cortical regions, and mixed differences in surface area (see Figure 1 for effect sizes and a graphical overview; see Table S3 in the online supplement for detailed results on all available regions, including sample sizes per region). These findings remained robust for most exploratory analyses (see Table S4 in the online supplement). However, when education level was included as an additional covariate, only subcortical volume differences in the caudate nucleus, putamen, and accumbens remained significant.

Notably, when the sample was divided into adults (>21 years; N=2,650) and children and adolescents (≤21 years; N=1,793), the majority of findings remained significant for adults, and additional group differences emerged for the insula, the banks

Quality Control Exclusion		Comorbidity		Other Exclusions		
Cortical	Subcortical	Psychosis	Bipolar	Healthy Controls With Disorder	Number of Included Images	Percent of Included Images
0	0	0	0	0	**52**	100.0
0	0	0	2	96	**498**	83.6
3	2	0	0	0	**25**	86.2
0	0	0	0	0	**15**	83.3
0	0	0	0	0	**12**	100.0
0	0	0	0	10[b]	**36**	78.3
1	1	0	0	0	**178**	97.8
0	0	0	0	6	**89**	93.7
2	4	0	0	0	**80**	93.0
7	13	0	0	0	**52**	72.2
0	0	0	0	0	**44**	100.0
0	0	0	0	0	**29**	100.0
0	1	0	0	0	**531**	99.8
0	1	0	0	0	**37**	97.4
2	3	0	0	0	**270**	98.2
1	4	0	0	0	**90**	93.8
0	1	0	0	0	**502**	99.0
0	0	0	0	0	**19**	95.0
4	6	43	4	0	**651**	90.8
0	0	0	0	0	**56**	98.2
0	0	0	0	0	**38**	100.0
0	0	0	0	0	**119**	100.0
0	55	0	3	238	**649**	66.4
0	0	0	0	0	**93**	100.0
0	0	0	0	0	**0**[c]	0.0
0	1	0	0	0	**7**	36.8
0	4	0	0	0	**73**	94.8
0	1	0	0	0	**46**	97.8
0	0	0	0	0	**18**	100.0
0	0	0	0	0	**87**	100.0
3	3	0	0	0	**28**	77.8
0	0	0	0	0	**23**	92.0
0	0	0	0	0	**0**	0.0
23	**99**	**43**	**9**	**343**	**4,443**	**87.9**

of the superior temporal sulcus, the entorhinal cortex, and the temporal pole (see Table S5 in the online supplement). Conversely, no group differences emerged for children and adolescents in any regions in the comparison of the specific phobia and control groups. The age-by-diagnosis analysis across the whole range of age found no significant interactions between age and diagnosis.

Direct Comparison of Animal and BII Subtypes

The comparison of participants with the animal (N=739) and BII (N=182) subtypes showed a significant difference in one area included in our hypotheses, with the BII phobia group showing larger cortical thickness in the medial OFC. Additionally, there were further group differences in areas not included in the hypotheses for cortical thickness, namely, within the lateral occipital cortex, pars orbitalis, pars triangularis, pericalcarine cortex, posterior cingulate cortex, rostral middle frontal gyrus, superior frontal cortex, and frontal pole (Figure 2; see Table S6 in the online supplement for detailed results on all available regions, including sample sizes per region). Again, these findings overall remained robust when re-including outliers, excluding scanners with fewer than 10 participants, excluding additional comorbidities, excluding subjects with psychotropic medication, using unilateral instead of bilateral data, and including education level as an additional covariate (see Table S7 in the online supplement). The results were less robust when including only participants with a formal diagnosis of specific phobia, when restricting specific phobia participants to those taking medication, and when including only participants with current specific phobia (see Table S7 in the online supplement). However, these follow-up examinations had to use considerably reduced animal and BII phobia sample sizes.

Again, dividing the sample of subtypes into adults (N=605) and children and adolescents (N=316) had a considerable effect. For adults, group differences in the medial OFC and most other regions remained significant, and additional thickness differences in the transverse temporal gyrus emerged (see Table S8 in the online supplement). Similar to the main analysis, no group differences emerged for the children and adolescents in any regions in the

TABLE 2. Sociodemographic characteristics of the sample used for the main analysis in a mega-analysis of brain alterations in specific phobia[a]

Study	Subtype						
	Specific Phobia (N)	Formal Diagnosis (N)	Animal Phobia (N)	BII Phobia (N)	Other/ Unknown (N)	Healthy Controls (N)	Total (N)
Barcelona	34	34	16	18	0	18	52
BHRCS	76	28	76	0	0	422	498
BION-SP	15	15	15	0	0	10	25
Bochum	15	15	0	15	0	0	15
COMIC	12	12	12	0	0	0	12
Czuwaj	25	0	12	13	0	11	36
Dresden CRC940C5	97	97	96	0	0	81	178
Dresden phobia subtypes	59	22	33	26	0	30	89
Graz	41	41	0	41	0	39	80
Graz II	25	25	0	25	0	27	55
Greifswald	20	0	20	0	0	24	44
Jena	14	14	14	0	0	15	29
Marburg FOR2107 MR	16	16	8	0	8	515	531
Münster FOR2107 MS	27	27	5	3	19	243	270
Münster SFBTRR-58 C09	90	90	85	0	5	0	90
Münster dental	18	0	0	18	0	19	37
Münster spider	29	29	29	0	0	473	502
PHOBIA EXPOSURE	19	19	19	0	0	0	19
PNC	319	319	0	0	319	332	650
Protect-AD	56	56	6	8	42	0	56
RepSpi	18	0	18	0	0	20	38
SDAN	47	47	0	0	47	72	119
SHIP	130	125	29	15	81	519	649
SMARTSCAN	46	46	46	0	0	47	93
SPIN NF	7	7	7	0	0	0	7
Teneriffa	34	34	34	0	0	39	73
Uppsala	46	0	46	0	0	0	47
Vanderbilt	9	9	2	0	7	9	18
Würzburg SFBTRR-58 C09	87	87	87	0	0	0	87
Würzburg spider	11	0	11	0	0	16	27
Würzburg spider II	13	0	13	0	0	10	23
Total	**1,452**	**1,213**	**739**	**182**	**528**	**2,991**	**4,443**

[a] BHRCS=Brazilian High Risk Cohort Study; BII phobia=blood-injection-injury phobia; BION-SP=Bender Institute of Neuroimaging; COMIC=COMIC Research/Leeds and York Partnership NHS Foundation Trust; Dresden CRC940C5=German Research Foundation (DFG) Collaborative Research Center 940, project C5; Marburg FOR2107 MR=DFG-Research Group 2107 Marburg site; Münster FOR2107 MS=DFG-Research Group 2107 Münster site; Münster SFBTRR-58 C09=DFG Collaborative Research Center Transregio 58, project C09, Münster site; PNC=Philadelphia Neurodevelopmental Cohort; Protect-AD=Providing Tools for Effective Care and Treatment of Anxiety Disorders consortium, specific phobia sample; SDAN=Section on Development and Affective Neuroscience; SHIP=Study of Health in Pomerania; Würzburg SFBTRR-58 C09=DFG Collaborative Research Center Transregio 58, project C09, Würzburg site.

comparison of the specific phobia and healthy control groups. The age-by-subtype analysis across the whole range of age did not find any significant interactions.

Comparison of Animal and BII Subtypes and Healthy Control Subjects

Given the considerable number of significant differences between the animal and BII subgroups in the previous analysis, we performed an exploratory comparison of both subtypes (animal, N=739; BII, N=182) with healthy control subjects (N=2,991), which was not specified in the preregistered analysis. These analyses found significant differences for the animal phobia group compared with the healthy control group in a large number of subcortical and cortical areas, including smaller volume in the caudate, putamen, and hippocampus and larger medial OFC cortical surface, consistent with effects in the main analysis of specific phobia compared with healthy control groups, and in other areas (Figure 3; see Table S9 in the online supplement for detailed results on all available regions, including sample sizes per region). Conversely, relatively few group differences emerged for the BII subgroup compared with the healthy control group. This included larger medial OFC cortical surface (Figure 3; see Table S10 in the online supplement for detailed results on all available regions, including sample sizes per region).

Dimensional Effects of Phobia Severity, Trait Anxiety, and Depression Severity

No significant associations with phobia severity, trait anxiety, or depression severity emerged for any area, either across all phobia participants or in the animal or BII phobia

All						Specific Phobia						Healthy Control Subjects					
Sex	Age (years)			Education (years)		Sex	Age (years)			Education (years)		Sex	Age (years)			Education (years)	
Female (%)	Mean	SD	Range	Mean	SD	Female (%)	Mean	SD	Range	Mean	SD	Female (%)	Mean	SD	Range	Mean	SD
88.5	22.1	2.7	18–29	NA	NA	88.2	22.2	2.6	18–29	NA	NA	88.9	21.7	2.8	18–29	NA	NA
45.2	9.5	1.9	5–14	4.0	1.7	43.4	9.2	1.7	6–13	3.7	1.5	45.5	9.5	1.9	5–14	4.1	1.7
92.0	23.6	3.1	18–31	NA	NA	86.7	23.5	3.3	18–31	NA	NA	100.0	23.8	3.0	19–28	NA	NA
46.7	39.3	10.7	27–60	NA	NA	46.7	39.3	10.7	27–60	NA	NA	NA	NA	NA	NA	NA	NA
83.3	28.2	9.6	17–42	NA	NA	83.3	28.2	9.6	17–42	NA	NA	NA	NA	NA	NA	NA	NA
77.8	23.0	4.2	19–38	NA	NA	92.0	23.0	4.8	19–38	NA	NA	45.5	23.2	2.3	20–27	NA	NA
91.6	24.7	6.1	17–48	12.5	1.1	92.8	25.4	6.8	17–48	12.3	1.3	90.1	23.8	5.1	18–44	12.9	0.6
77.5	23.7	4.7	18–46	12.4	0.7	78.0	23.9	5.0	18–46	12.3	0.8	76.7	23.1	4.1	18–38	12.5	0.5
60.0	29.7	9.9	19–62	12.6	1.0	61.0	30.1	10.7	20–62	12.6	1.1	59.0	29.2	9.0	19–53	12.7	0.9
55.8	29.6	10.2	20–56	NA	NA	56.0	33.6	11.5	23–56	NA	NA	55.6	25.9	7.1	20–48	NA	NA
100.0	22.3	3.0	18–29	13.0	0.0	100.0	21.9	2.9	18–28	13.0	0.0	100.0	22.7	3.1	19–29	13.0	0.0
100.0	24.8	6.1	19–49	NA	NA	100.0	24.4	4.1	21–35	NA	NA	100.0	25.2	7.7	19–49	NA	NA
59.5	34.8	12.7	18–65	13.7	2.6	62.5	32.6	14.3	18–59	11.4	2.1	59.4	34.9	12.7	18–65	13.8	2.6
64.8	29.4	11.2	18–65	14.3	2.3	74.1	36.1	13.5	19–64	14.8	2.7	63.8	28.6	10.7	18–65	14.2	2.2
83.3	28.3	9.3	18–56	14.7	2.8	83.3	28.3	9.3	18–56	14.7	2.8	NA	NA	NA	NA	NA	NA
81.1	28.0	10.3	18–60	12.8	1.0	88.9	29.6	11.0	19–53	12.7	1.2	73.7	26.5	9.6	18–60	12.9	0.9
54.6	37.3	11.8	18–59	15.3	2.4	86.2	25.1	5.5	18–39	NA	NA	52.6	38.1	11.7	18–59	15.3	2.4
100.0	23.3	3.1	19–29	NA	NA	100.0	23.3	3.1	19–29	NA	NA	NA	NA	NA	NA	NA	NA
56.7	14.6	3.8	8–23	7.8	3.6	64.9	14.3	3.6	8–21	7.4	3.4	48.6	14.9	3.9	8–23	8.2	3.8
57.1	34.6	13.3	18–67	NA	NA	57.1	34.6	13.3	18–67	NA	NA	NA	NA	NA	NA	NA	NA
84.2	23.4	4.2	18–43	NA	NA	100.0	24.1	5.9	19–43	NA	NA	70.0	22.9	1.8	18–26	NA	NA
61.3	13.1	2.9	8–18	7.2	2.9	66.0	11.9	2.9	8–18	6.3	2.9	58.3	13.7	2.8	8–18	7.9	2.8
56.6	55.5	12.5	31–90	10.5	1.4	79.2	50.8	10.1	31–76	10.5	1.4	50.9	56.7	12.8	31–90	10.5	1.4
86.0	20.7	2.1	16–25	12.9	0.4	91.3	20.5	2.3	16–25	12.9	0.4	80.9	20.9	1.9	16–25	12.9	0.4
100.0	21.7	2.4	19–26	14.7	0.8	100.0	21.7	2.4	19–26	14.7	0.8	NA	NA	NA	NA	NA	NA
71.2	27.9	11.0	18–56	NA	NA	82.4	35.1	11.9	19–56	NA	NA	61.5	21.7	4.6	18–41	NA	NA
73.9	26.0	7.5	20–55	NA	NA	73.9	26.0	7.5	20–55	NA	NA	NA	NA	NA	NA	NA	NA
77.8	20.4	3.9	10–25	16.0	1.3	77.8	20.3	3.6	12–25	16.1	1.5	77.8	20.4	4.3	10–25	15.9	1.2
85.1	28.6	8.5	18–60	12.0	1.5	85.1	28.6	8.5	18–60	12.0	1.5	NA	NA	NA	NA	NA	NA
100.0	22.0	3.7	18–37	NA	NA	100.0	21.7	5.3	18–37	NA	NA	100.0	22.2	2.3	18–26	NA	NA
78.3	26.7	6.8	19–42	11.6	1.2	76.9	29.5	7.5	21–42	11.2	1.2	80.0	23.0	3.1	19–29	12.1	0.9
62.7	**29.0**	**16.9**	**5–90**	**10.8**	**4.3**	**75.3**	**25.2**	**13.2**	**6–76**	**10.1**	**3.9**	**56.7**	**30.8**	**18.1**	**5–90**	**11.1**	**4.4**

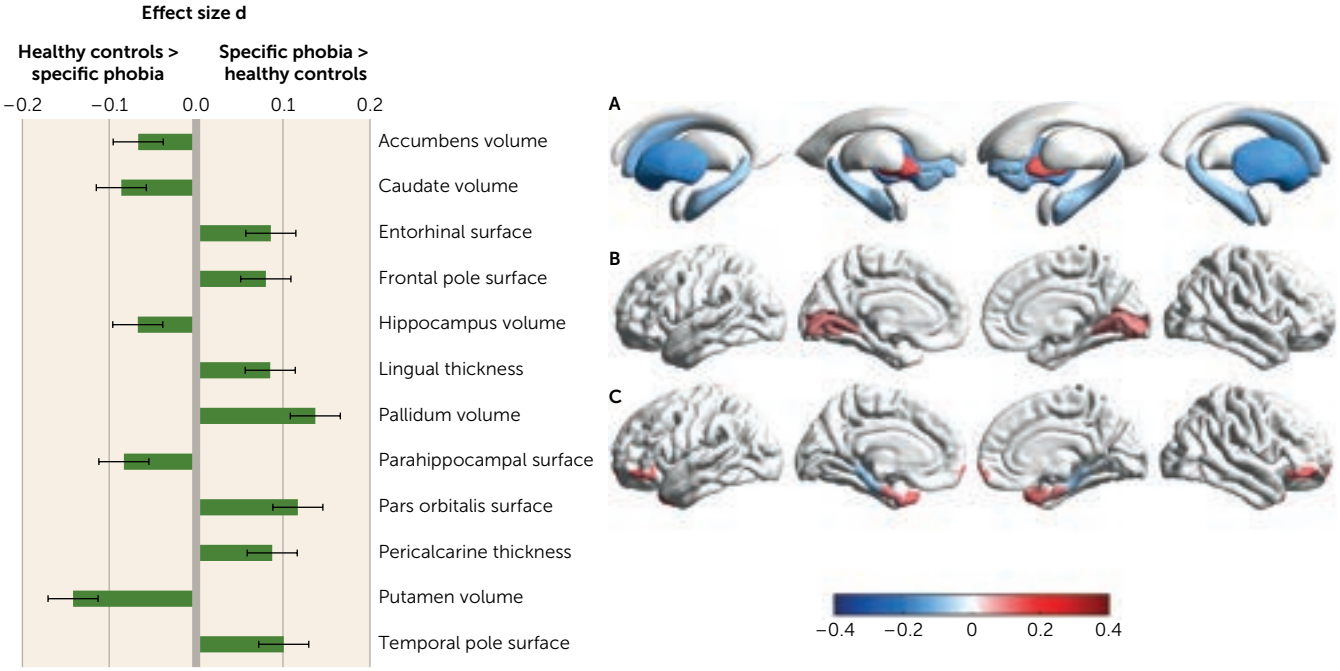
subgroups separately (phobia severity: all, N=825; animal, N=614; BII, N=164; trait anxiety: all, N=809; animal, N=451; BII, N=50; depression severity: all, N=622; animal, N=399; BII, N=69). As there was also sufficient variability in trait anxiety within the healthy control group, we performed an additional analysis in this group to examine the impact of trait variability in a normative group (N=1,755), which also yielded no significant results.

DISCUSSION

We have presented results of a preregistered analysis from the ENIGMA Anxiety Working Group that examined brain structure differences between individuals with specific phobia and healthy control subjects, as well as between two phobia subtypes, between different age groups, and in relation to anxiety and depression severity. We found group differences between individuals with specific phobia and healthy control subjects in most subcortical areas, including the hippocampus, caudate, putamen (smaller volume in specific phobia), and pallidum (larger volume in specific phobia) and multiple cortical areas. These group differences were largely driven by participants with animal phobia, not those with BII phobia. Comparing these two subgroups directly, we found larger cortical thickness in the medial OFC in participants with BII phobia, in line with our a priori hypotheses, and in other cortical areas. We did not find associations between brain structure and symptom severity. Finally, all findings occurred exclusively in adult participants, not in children and adolescents.

Group differences between participants with specific phobia and healthy control subjects, which were largely driven by participants with animal phobia, exceeded those reported for generalized anxiety disorder and social anxiety disorder in extent and effect size in comparable analyses (31, 32). Notably, these group differences were not limited to smaller volume, surface area, and thickness but also included enlarged areas, contrary to other ENIGMA studies within the internalizing spectrum, such as in obsessive-compulsive disorder and major depression (33, 34). While these findings implicate notable brain structure alterations in specific phobia, they appear to be minimally related to our a priori

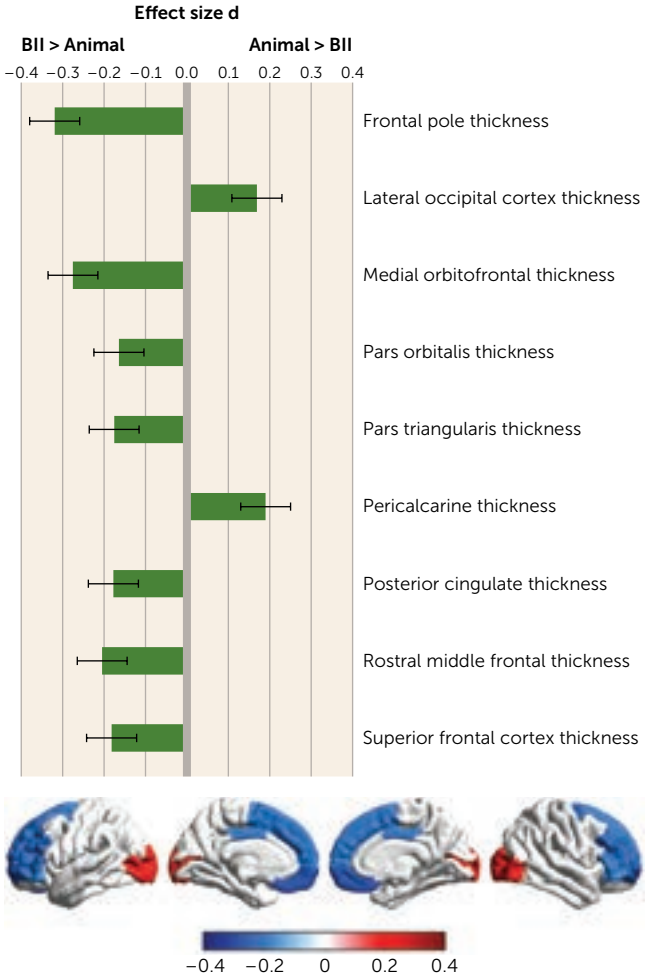
FIGURE 1. Significant differences between participants with specific phobia and healthy control subjects in a mega-analysis of brain alterations in specific phobia[a]



[a] The bar chart shows effect sizes between groups of individuals with specific phobia and healthy control subjects; error bars indicate standard error. Positive effect sizes signify larger volume, surface area, and thickness in the specific phobia group compared with the healthy control group. The images on the right show the significant differences in the brain. Panel A shows subcortical volumes, panel B cortical thickness, and panel C cortical surface area.

hypotheses. Furthermore, they showed no overlap with major regions emphasized in functional activation maps for specific phobia (7, 8), no overlap with structural alterations commonly associated with general psychopathology (35), and no overlap with the regions commonly selected as regions of interest in previous studies of specific phobia (9–11). A previous whole-brain investigation similarly failed to detect specific-phobia-related differences in regions such as the amygdala, thalamus, and insula (18). This suggests that specific-phobia-related alterations in brain structure may not match the amygdalocentric perspective that prevailed in functional research for some time. Furthermore, it raises the question of the degree to which specific-phobia-related alterations in brain structure are related to alterations in neural activation. While the relationship between structural and functional brain alterations is not yet fully understood, initial evidence suggests that structural alterations first occur in central hub regions of the brain and then propagate along functional (and, less clearly, anatomical and genetic) connectivity patterns (36). A promising candidate for explaining this pattern is nodal stress (36). Nodal stress suggests that brain hub regions are particularly strained as a result of strong network activity and may first show disorder-associated alterations (37). This mechanism in turn suggests that functional alterations precede structural changes in the same regions, and thus disorder-associated functional and structural maps should show considerable overlap. This is only partially evident in the comparison of structural alterations found in the present study with functional changes noted in previous meta-analyses of specific phobia (e.g., altered activation in the hippocampus, putamen, caudate, and lingual gyrus [7], but not with major regions such as the dorsal ACC or anterior insula, as discussed above). However, such comparisons are hindered by the limited sample sizes on which meta-analyses of functional changes in specific phobia are based, well below the sample size of the present study. The impression that the relationship of structural to functional changes in specific phobia is not yet fully understood is additionally strengthened by the lack of any significant correlations between brain structure and phobia or trait anxiety severity in our study, as opposed to previous functional studies that reported such associations (16, 38). At the same time, our findings do newly implicate various subcortical structures in the neuroanatomy of specific phobia, with most subcortical regions showing significantly different, and mostly reduced, volumes in individuals with specific phobia compared with healthy control subjects. Interestingly, similar subcortical differences in the putamen and pallidum have been found in an ENIGMA Anxiety Working Group study on social anxiety disorder (32). Additionally, we observed a nonsignificant inverse association of subcortical volume in the pallidum with depression severity in the present analysis. Together, these results suggest that the reported subcortical differences may be at least partly related to broader internalizing psychopathology instead of being a specific neural substrate of specific phobia. The present results also underscore the need

FIGURE 2. Significant differences between individuals with animal phobia and individuals with blood-injection-injury (BII) phobia[a]



[a] The bar chart shows effect sizes between groups of individuals with animal phobia and BII phobia; error bars indicate standard error. Positive effect sizes signify larger volume, surface area, and thickness in individuals with animal phobia compared with those with BII phobia. The images below the graph show the significant differences in cortical thickness between the groups with animal phobia and BII phobia.

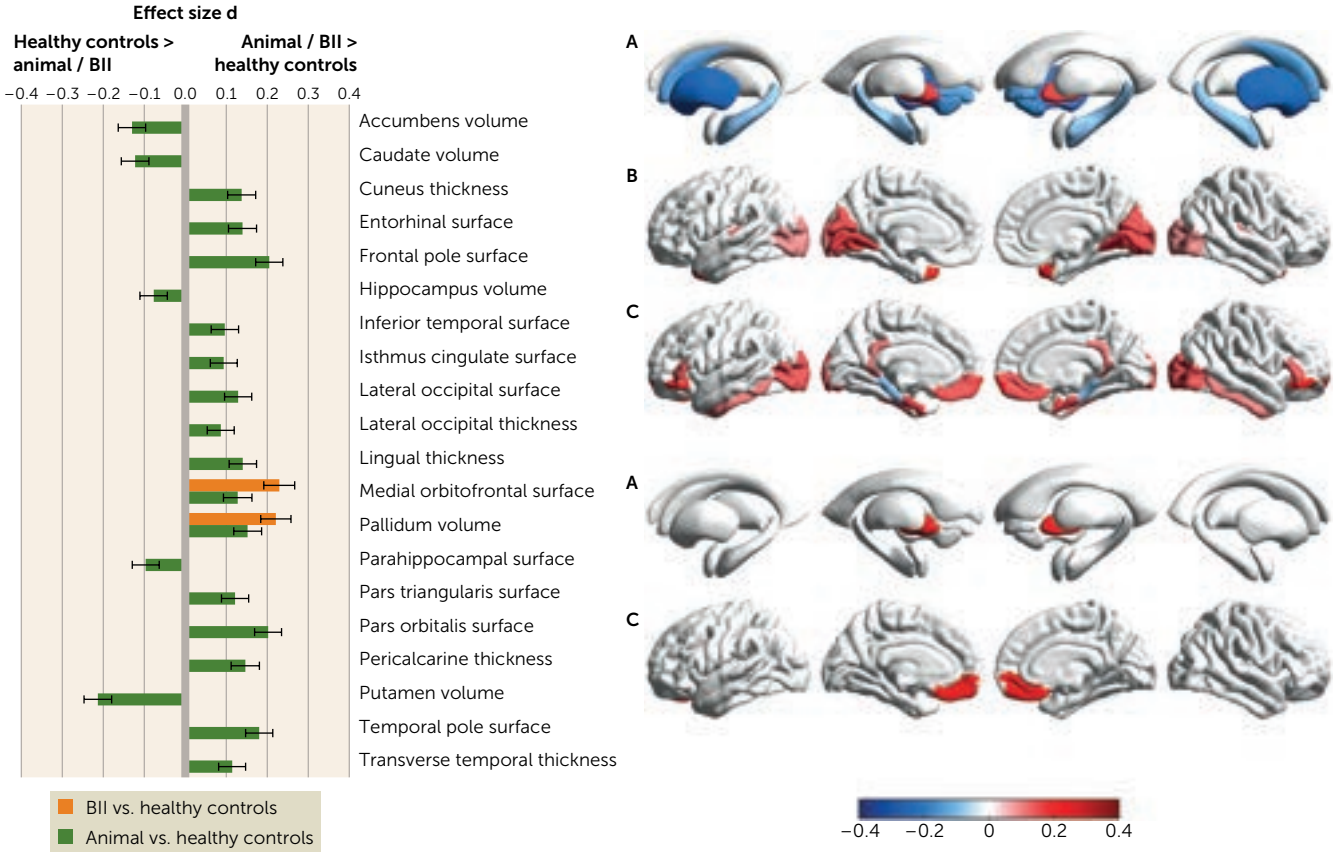
to complement analyses using preselected regions of interest with whole-brain examinations of brain structure in specific phobia in future studies, and the importance of having sufficient statistical power for these kinds of analyses.

Direct comparisons between phobia subgroups showed significant differences between participants with animal phobia (N=739) and BII phobia (N=182) in a variety of cortical regions, including the medial OFC, where the animal phobia subgroup showed lower cortical thickness. These results fit with previous results showing increased volumes (18) in BII compared with animal phobia in orbitofrontal regions, and they align with the idea of fear processing in BII phobia involving larger impairment during cognitive processes such as stimulus appraisal and evaluation (17, 39) and emotion regulation (39, 40). For other areas implicated in our a priori hypotheses, particularly the amygdala and the thalamus, functional differences between phobia groups were also common in earlier studies (15, 16, 38, 40), but both areas exhibited only nonsignificant group differences in our analysis. Additionally, in our analysis, volume and cortical thickness in these areas were not related to phobia severity in or across subgroups. Thus, the present results provide evidence that phenomenological differences between specific phobia subgroups also relate to divergent neural underpinnings, but more research is needed to understand the exact functional implications of this finding, particularly regarding the less sympathetically mediated, sometimes even diphasic fear response in the BII subtype.

In this study, although we examined data on phobia-related differences in brain structure in children and adolescents, all group differences were found exclusively in the adult subsamples. Although this is in line with an ENIGMA Anxiety Working Group study on social anxiety disorder (32), it was a surprising finding given that disorder onset early in childhood is so common (4) and given that neurofunctional and structural correlates are observed in individuals with other anxiety disorders, and even in youths at risk for anxiety disorders (41). However, adults may have substantially higher levels of disorder persistence compared with children and adolescents, as specific phobia cases typically begin in childhood (4), but most will remit before adulthood (42). Alternatively, the finding could be associated with increased overall psychopathology load in adulthood, or with subtle neuroanatomical correlates of specific phobia during youth that disappear against the predominant age-related changes and brain variability. Further research is needed on the trajectory of phobia-associated alterations over the developmental span, and taking into account disorder duration and persistence, to elucidate this null finding. Finally, this null finding may also be influenced by lower statistical power for children and adolescents in the disorder subtype analyses. For the main comparison of participants with specific phobia versus healthy control subjects, however, we did not find indications of substantially lower power for children and adolescents compared with adults.

Although our overall sample size in this study substantially exceeded previous sample sizes in examinations of brain structure alterations associated with specific phobia, sample sizes remained moderate for individual analyses, particularly regarding the phobia subgroups. Specifically, in our analysis, which includes substantial data that have never been analyzed with respect to specific phobia, animal phobia was almost four times more common than BII phobia. This translates to significantly more statistical power and may explain the predominance of animal-phobia-associated findings for the complete sample. Additionally, despite using established ENIGMA protocols and procedures, harmonization of this wealth of data is possible only to a limited degree. Particularly, site-specific scanners and scan sequences, FreeSurfer versions, raters for quality control, and differences in phobia severity questionnaires may create systematic variation in the data, unrelated to group membership. We aimed to model site-specific scanners and scan sequences within our analytic approach, but residual effects may remain,

FIGURE 3. Significant differences between individuals with animal phobia or blood-injection-injury (BII) phobia and healthy control subjects[a]



[a] The bar chart shows effect sizes between groups of individuals with animal phobia and healthy control subjects and between individuals with BII phobia and healthy control subjects; error bars indicate standard error. Positive effect sizes signify larger volume, surface area, and thickness in the respective phobia subgroup compared with healthy control subjects. The graphical depiction on the right shows the significant differences in the brain between individuals with animal phobia and healthy control subjects (upper right) and between individuals with BII phobia and healthy control subjects (lower right). The panels labeled "A" show subcortical volumes, the panel labeled "B" shows cortical thickness, and the panels labeled "C" show cortical surface area.

particularly as sample sizes per scanner were considerably imbalanced, which may have influenced parameter estimates particularly for scanners with few participants. Sites also used a variety of phobia severity questionnaires, which we aimed to ameliorate by transforming data into site-specific centiles, but this procedure naturally leads to information loss.

In summary, our findings implicate brain structure alterations in specific phobia, although subcortical alterations in particular may also relate to broader internalizing psychopathology. Subgroup-specific analyses support the idea that phenomenological differences between subgroups also relate to diverging neural underpinnings, with brain areas that are related to higher cognitive processes being particularly implicated in BII phobia. Interestingly, specific-phobia-related differences emerged for adults but not for children or adolescents. This may be due to stronger levels of disorder persistence, increasing overall psychopathology load in adult patients, or age-related developmental changes in the brain. Examining and disentangling the age-related and disorder-course-related trajectories of specific phobia in the brain may be a promising avenue for further research. Additionally, future analyses of resting-state data may provide valuable insights into the role of large-scale brain circuits. Overall, brain structure in specific phobia is understudied, and its role in the etiopathogenesis of the disorder is not well understood. This work is a starting point for further investigations on the role of brain morphometric alterations for our understanding and treatment of specific phobia.

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