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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

Running Title: ENIGMA mega-analysis in specific phobia

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Abstract

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 subjects with specific phobias and healthy controls as well as between animal and blood-injection-injury (BII) subtypes. Additionally, the authors investigated associations of brain structure with symptom severity and age (youth vs. adults).

Methods: Datasets from 31 original studies were combined to create a final sample with n_{phobia}=1452 phobia subjects and $n_{control}$=2991 healthy participants (62.7% female, 5-90yrs). Imaging processing and quality control were conducted using established ENIGMA-protocols. Subcortical volumes as well as cortical surface area and thickness were examined in a preregistered analysis (osf.io/n6bhz).

Results: Phobia subjects compared to healthy controls showed mostly smaller subcortical volumes, mixed surface differences and larger cortical thickness across a substantial number of regions. Phobia subgroups also showed differences, including, as hypothesized, larger medial orbitofrontal cortex thickness in BII phobia compared to animal phobia (n_{BII}=182; n_{animal}=739). All findings were driven by adult subjects; the authors found no significant results 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.

Keywords

Specific Phobia, Animal phobia, Blood-Injection-Injury phobia, structural neuroimaging, mega-analysis, ENIGMA

Introduction

Specific phobia is the most prevalent anxiety disorder (1, 2), with global lifetime prevalence ranging between 2.6-12.5% (3). According to the 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 future 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, insula, thalamus and 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 (7)), fear conditioning (amygdala (5)), emotion regulation (anterior cingulate (5)) and impaired emotion appraisal (inferior frontal gyrus (8)). The current paper complements these functional correlates by reporting findings from a large, multi-site investigation examining neuroanatomical correlates of specific phobia.

In contrast to functional MRI investigations, few studies 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). As 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 anterior cingulate cortex (ACC) and thalamus for the animal subtype, but are less clear-cut for the BII subtype (15-17). In contrast, the orbitofrontal cortex (OFC) has been implicated for BII phobia (15, 17). Given the paucity of research on brain structure associated with specific phobia, it remains unclear if these

subtypes indeed manifest unique neurostructural correlates corresponding to functional activation patterns.

The few available preliminary findings indicate 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 their early onset during childhood, few studies examine brain structure related to specific phobia before adulthood. Third, previous research on anxiety disorders demonstrated that the presence of depressive comorbidity altered gray matter volumes (20). However, it is unclear whether comorbid depressive symptoms also influence brain structure associated with specific phobia.

This investigation aims to address these gaps by comparing brain structure in subjects with specific phobia and healthy subjects. Within the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) collaboration (21), the ENIGMA-Anxiety Working Group (22) obtained 33 datasets with information on neurostructural correlates of specific phobia and its animal and BII subtypes of which 31 datasets (age range 5-90 years) were included. We examine the following hypotheses: 1) Compared to healthy controls, specific phobia subjects 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) animal phobia subjects would show altered amygdala and thalamus volumes when compared to healthy controls or BII phobia subjects, while BII phobia subjects will show altered cortical thickness and surface area in OFC areas when compared to healthy controls or animal phobia subjects. 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 a hypothesis on the relationship with age.

Materials and Methods

Samples

We collected datasets from 33 original datasets acquired on 43 distinct MRI scanners. We included datasets with initially at least 10 subjects with SPH, while datasets with fewer subjects were excluded in total, leading to the inclusion of 31 of the collected datasets. Subjects were included with 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 cut-off 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 controls. All participants provided written informed consent when participating in the original studies, and these original studies acquired positive evaluation by institutional review boards and ethic committees. The current study was preregistered at the Open Science Framework (osf.io/n6bhz).

This project depended on datasets 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 current analysis provides unprecedented statistical power and heterogeneity regarding the number of participants included with specific phobia.

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 T1-weighted MR images) so that we performed the processing centrally. Imaging processing and quality control were in both cases conducted 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 laterality and to calculate surface area and cortical thickness data for thirty-four cortical regions per laterality and the total intracranial volume. Cortical region segmentation was performed according to the Desikan-Killiany cortical atlas (26). Resulting segmentations were checked visually for substantial over- or underestimation; this process was supported by summary statistics, boxplots, 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 was excluded.

Statistical Analysis

FreeSurfer-derived data for cortical and subcortical regions was used as input in a linear mixed model on R version 4.0.4 including disorder state (specific phobia, healthy controls) as variable of interest and age, sex and intracranial volume (ICV) as fixed factors and scanner as random intercepts (supplemental table 1 provides an overview on scanner characteristics and a description of procedures for grouping subjects across studies for this covariate). Here, we deviated from the preregistration 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 non-significant areas. To limit multiple testing against the background of the large number of regions, left and right side cortical thickness, surface area and subcortical volumes were averaged. 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). Standard errors and effect sizes were calculated according to Nakagawa and Cuthill (2007; 28).

A second preregistered analysis was conducted to test for structural correlates specifically for the subtypes (hypothesis 2). This approach was limited to animal and BII subtypes (including dental phobia) for whom sufficient data for subtype analysis was available (n_{BII}=182; n_{animal}=739; supplemental figure 1). 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 specific phobia subjects with a single subtype, not with multiple subtypes. As this analysis yielded interesting results, we conducted two additional post-hoc analyses with animal phobia subjects vs healthy controls and BII phobia subjects vs healthy controls, which were not included in the preregistration.

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

Accompanying these main analyses, we conducted further exploratory analyses on robustness of the results by testing whether areas still showed significant differences between groups when using specific phobia subjects with formal diagnosis only, using subjects with current specific phobia only, using specific phobia and healthy controls subjects with and without medication only, examining adults (>21 years) only and children and adolescents (≤ 21 years) only, excluding subjects from scanners with less than ten participants, excluding subjects additional comorbidities, and examining the impact of education, re-including outliers, and unilateral vs bilateral regions (for details see supplemental methods). Given the diverging findings for the age groups in the adults only and children and adolescents only analyses, we added further exploratory analyses on an age-by-diagnosis interaction (details also in the supplemental methods).

Results

We received data from n=5330 individuals. Table 1 provides detailed information on the amount and reason of excluded subjects. The final sample consisted of n=4443 participants, with n_{phobia}=1452 specific phobia subjects and $n_{control}$=2991 healthy controls. Sociodemographic information can be found in table 2, and supplemental table 2 shows current and lifetime comorbidities within specific phobia subjects. Compared regarding sociodemographic variables, specific phobia subjects included significantly less males, were significantly younger, and had significantly fewer years of education compared to healthy controls (all ps < 0.001).

[Tables 1-2]

Specific phobia subjects versus healthy controls

The main group comparison showed significantly smaller subcortical volumes for specific phobia (n=1452) vs healthy controls (n=2991) in several regions including the caudate, putamen and hippocampus, significantly larger thickness in several cortical regions and mixed alterations in surface area (figure 1 for effect sizes and graphical overview; supplemental table 3 for detailed results on all available regions including sample sizes per region). These findings remained robust for most exploratory analyses (supplemental table 4). However, when including education as an additional covariate, only subcortical volume differences in the caudate nucleus, putamen, and accumbens remained significant.

Crucially, when splitting the sample into adults (>21 years; n=2650) and children to adolescents (=<21 years; n=1793), the majority of findings remained significant in adults, and additional group differences emerged for the insula, banks superior temporal sulcus,the entorhinal cortex and the temporal pole (supplemental table 5). Conversely, no group differences emerged for any regions for the comparison of specific phobia vs healthy controls in children to adolescents. The age-by-

diagnosis analysis across the whole range of age found no significant interactions between age and diagnosis.

[Figure 1]

Direct comparison of animal and BII subtypes

The comparison of animal (n=739) versus BII phobia (n=182) subjects showed a significant difference in one area included in our hypotheses, with BII phobia subjects 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, posterior cingulate, rostral middle frontal, superior frontal cortex and frontal pole (figure 2; supplemental table 6 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 <10 participants, excluding additional comorbidities, excluding subjects with psychotropic medication, using unilateral instead of bilateral data, and adding education as an additional covariate (supplemental table 7). Results were less robust, when allowing only for subjects with a formal diagnosis of specific phobia, restricting specific phobia subjects to those taking medication, and when allowing only for subjects with current specific phobia (supplemental table 7). However, these follow-up examinations had to use considerably reduced animal and BII phobia sample sizes.

Again, splitting the sample of subtypes in adults (>21 years; n=605) and children and adolescents (=<21 years; 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 (supplemental table 8). Similar to the main analysis, no group differences emerged for any regions for the comparison of specific phobia vs healthy controls for the children to

adolescents. The age-by-subtype analysis across the whole range of age did not find any significant interactions.

[Figure 2]

Comparison of animal and BII subtypes versus healthy controls

Given the considerable number of significant differences between the animal and BII subgroups in the previous analysis, we performed an additional, exploratory comparison of both subtypes (n_{animal}=739; n_{BII}=182) with healthy controls (n=2991) which was not specified in the preregistration. These analyses found significant differences for animal phobia compared to healthy controls 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 vs healthy controls and further areas (figure 3, yellow; supplemental table 9 for detailed results on all available regions including sample sizes per region). Conversely, only relatively few group differences emerged for BII phobia subjects against healthy controls. This included larger medial OFC cortical surface (figure 3, blue; supplemental table 10 for detailed results on all available regions including sample sizes per region).

[Figure 3]

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 - neither across all phobia subjects nor in animal or BII phobia subjects separately (phobia severity: n_{all} = 825, n_{animal} = 614, n_{bii} = 164; trait anxiety: n_{all} = 809, n_{animal} = 451, n_{bii} = 50; depression severity: n_{all} = 622, n_{animal} = 399, n_{bii} = 69). As there was also sufficient variability in trait anxiety within

457 the healthy controls, we conducted an additional analysis in this group to examine the impact of trait
458 variability in a normative group (n=1755), which also yielded no significant results.
459
460 **Discussion**
461 We here present a preregistered analysis from the ENIGMA-Anxiety Working Group that examined
462 brain structure differences between subjects with specific phobia and healthy controls, as well as
463 between two phobia subtypes, between different age groups, and in relation to anxiety and
464 depression severity. We found group differences between specific phobia and healthy controls in
465 most subcortical areas including the hippocampus, caudate, putamen (smaller volume in specific
466 phobia) and pallidum (larger volume in specific phobia), and multiple cortical areas. These group
467 differences were largely driven by animal phobia but not BII phobia subjects. Comparing these two
468 subgroups directly, we found larger cortical thickness in the medial OFC in BII phobia subjects in line
469 with a-priori hypotheses, and in further cortical areas. We did not find associations between brain
470 structure and symptom severity. Finally, all findings occurred exclusively in adult subjects but not in
471 children and adolescents.

472 Group differences between specific phobia and healthy controls, which were largely driven by
473 animal phobia subjects, exceeded those reported for Generalized Anxiety Disorder and Social
474 Anxiety Disorder in comparable analyses in extent and effect size (31, 32). Notably, these group
475 differences were not limited to smaller volume, surface area and thickness, but also included
476 enlarged areas, contrary to other ENIGMA studies within the internalizing spectrum, such as in
477 Obsessive-Compulsive Disorder or Major Depression (33, 34). While these findings implicate notable
478 brain structure alterations in specific phobia, they appeared minimally related to our a-priori
479 hypotheses. Furthermore, they showed no overlap with major regions emphasized in functional
480 activation maps for specific phobia (7, 8), no overlap with structural alterations commonly
481 associated with general psychopathology (35) and no overlap with the regions commonly selected as
482 ROIs in prior studies of specific phobia (9-11). Similar to our results, a previous whole-brain

investigation also 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. Further, it raises the question to what degree 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 fully understood yet, 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 (41). A promising candidate for explaining this pattern is nodal stress (41). Nodal stress suggests that brain hub regions are particularly strained due to strong network activity and may first show disorder-associated alterations (42). This potential mechanism suggests that functional alterations precede structural changes in the same regions, thus disorder-associated functional and structural maps should show considerable overlap. This is only partially evident in the comparison of structural changes from our study to functional changes from meta-analyses to date (e.g. altered activation in the hippocampus, putamen, caudate and lingual gyrus in (7), but not with major regions such as the dorsal ACC or anterior insula as discussed above). However, comparing these structural and functional alterations is hindered by the fact that meta-analyses of functional changes in specific phobia to date are based on very limited sample sizes, well below the sample size of our current 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 which reported such associations (16, 36). At the same time, our findings do implicate various new subcortical brain structures in the neuroanatomy of specific phobia, with most subcortical regions showing significantly different, and mostly reduced, volumes in specific phobia compared to healthy controls. Interestingly, similar subcortical differences in the putamen and pallidum have been found in a related ENIGMA-Anxiety Working Group study on Social Anxiety Disorder (32). Additionally, there was a nonsignificant trend for

subcortical volume in the pallidum to be inversely associated with depression severity in our current analysis. Together, these results suggest that the reported subcortical differences may at least partly be related to broader internalizing psychopathology instead of being a specific neural substrate of specific phobia. The current results also underscore the need to complement analyses with pre-selected ROIs with more whole-brain examinations of specific phobia brain structure in future studies, and the importance of being sufficiently powered for these kinds of analysis.

Direct comparisons between phobia subgroups showed significant differences between animal (n_{animal}=739) and BII phobia (n_{BII}=182) in a variety of cortical regions including the medial OFC, where animal phobia subjects showed lower cortical thickness. These results fit with previous results of increased volumes (18) in BII compared to animal phobia in orbitofrontal regions, and align with the idea of fear-processing in BII phobia involving impairment during cognitive processes such as stimulus appraisal and evaluation (17, 37) and emotion regulation (37, 38) to a larger extent. For other areas implicated in our a-prior hypotheses, particularly the amygdala and thalamus, functional differences between phobia groups were also common in earlier studies (15, 16, 36, 38), but both areas exhibited only non-significant trends in our analysis. Additionally, in our analysis, volume and cortical thickness in these areas were not related to phobia severity in or across subgroups. In conclusion, the current results further provide evidence that phenomenological differences between subgroups also relate to diverging 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.

The current study examined data on phobia-related differences in brain structure in children and adolescents. However, all group differences were exclusively found in the adult subsamples. Although this is in line with ENIGMA-Anxiety study on Social Anxiety Disorder (32), this was a surprising finding given that disorder onset early during childhood is so common (4) and given that other anxiety disorders and even youth at risk for anxiety disorders appear to be accompanied by

534 neurofunctional and –structural correlates (39). However, adults may have substantially stronger
535 levels of disorder persistence compared to children and adolescents, as specific phobia cases
536 typically begin in childhood (4) but most will remit before adulthood (40). Alternatively, the finding
537 could be associated with increased overall psychopathology load during adulthood, or with subtle
538 neuroanatomical correlates of specific phobia during youth that disappear against the predominant
539 age-related changes and brain variability. Future research on the trajectory of phobia associated
540 alterations over the developmental span and taking into account disorder duration and persistence
541 is needed to elucidate this null finding. Finally, this null finding might also be influenced by smaller
542 power for children and adolescents in the disorder subtype analyses. For the main comparison of
543 specific phobia vs healthy controls however, we did not find indications of substantially lower power
544 in children and adolescents compared to adults.

545 We here report an examination of brain structure alterations associated with specific phobia
546 substantially exceeding previous sample sizes. Still, sample sizes remained moderate for individual
547 analyses, particularly regarding the phobia subgroups. Additionally, despite using established
548 ENIGMA protocols and procedures, harmonization of this wealth of data is only possible to a limited
549 degree. Particularly site-specific scanners and scan sequences, FreeSurfer versions, raters for quality
550 control and differences in phobia severity questionnaires may induce systematic variation in the
551 data unrelated to group membership. We aimed to model site-specific scanners and scan sequences
552 within our analytic approach, but residual effects may remain, particularly as sample sizes per
553 scanner were considerably imbalanced. This might have influenced parameter estimates particularly
554 for scanners with only few participants. Sites also used a variety of different phobia severity
555 questionnaires, which we aimed to ameliorate by transforming data into site-specific centiles, but
556 this procedure naturally leads to information loss.

557 In conclusion, we here present a preregistered analysis by the ENIGMA-Anxiety Working Group on
558 brain structure associated with specific phobia. Our findings implicate brain structure alterations in

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

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Figure legends

FIGURE 1. Significant differences between specific phobia subjects and healthy controls[a]

[a]The bar chart (left) provides effect sizes between groups of individuals with specific phobia and healthy controls, error bars are standard errors. Positive effect sizes signify larger volume, surface area and thickness in specific phobia compared to healthy controls. The graphical depiction (right) shows the significant differences in the brain. Panel (A) shows subcortical volumes, panel (B) cortical thickness and panel (C) cortical surface area.

FIGURE 2. Significant differences between animal phobia subjects and BII phobia subjects[a]

[a]The bar chart (above) provides effect sizes between groups of individuals with animal phobia and BII phobia, error bars are standard errors. Positive effect sizes signify larger volume, surface area and thickness in animal phobia subjects compared to BII phobia subjects. The graphical depiction (below) shows the significant differences in cortical thickness between animal phobia and BII phobia subjects.

FIGURE 3. Significant differences between animal phobia subjects and healthy controls and BII phobia subjects and healthy controls[a]

[a]The bar chart (left) provides effect sizes between groups of individuals with animal phobia subjects and healthy controls in green and between BII phobia subjects and healthy controls in orange. Error bars are standard errors. Positive effect sizes signify larger volume, surface area and thickness in the respective phobia subgroup compared to healthy controls. The graphical depiction (right) shows the significant differences between animal phobia subjects and HC (upper right) and BII phobia subjects

and HC (lower right) in the brain. Panel (A) shows subcortical volumes, panel (B) cortical thickness and panel (C) cortical surface area.

Table 1. Number of initial images, number of included images and reasons for exclusion by site.

	initial data				Freesurfer fail		quality control exclusion		Comorbidity		Other exclusion		
Study	initial datasets cortical	initial datasets subcortical	initial datasets covariates	initial datasets all complete	cortical	sub-cortical	cortical	sub-cortical	psychosis	bipolar	healthy controls with disorder	number of included images	percent of included images
Barcelona (38, 39)	52	52	52	**52**	0	0	0	0	0	0	0	**52**	100.0
BHRCS (40)	605	605	2511	**596**	0	0	0	0	0	2	96	**498**	83.6
BION-SP (41)	29	29	29	**29**	0	0	3	2	0	0	0	**25**	86.2
Bochum	18	18	18	**18**	1	2	0	0	0	0	0	**15**	83.3
COMIC (42)	12	12	12	**12**	0	0	0	0	0	0	0	**12**	100.0
Czuwaj (43)	46	46	48	**46**	0	0	0	0	0	0	10[a]	**36**	78.3
Dresden CRC940C5	187	187	182	**182**	2	0	1	1	0	0	0	**178**	97.8
Dresden Phobia Subtypes (23)	95	95	126	**95**	0	0	0	0	0	0	6	**89**	93.7
Graz (30)	86	86	86	**86**	0	1	2	4	0	0	0	**80**	93.0
Graz II (29)	72	72	72	**72**	0	0	7	13	0	0	0	**52**	72.2
Greifswald (44)	44	44	45	**44**	0	0	0	0	0	0	0	**44**	100.0
Jena (45)	29	29	30	**29**	0	0	0	0	0	0	0	**29**	100.0
Marburg FOR2107 MR (46, 47)	532	532	532	**532**	0	0	0	1	0	0	0	**531**	99.8
Muenster Dental (48)	38	38	38	**38**	0	0	0	1	0	0	0	**37**	97.4

Muenster FOR2107 MS (49)	275	275	275	**275**	0	0	2	3	0	0	0	**270**	98.2
Muenster SFBTRR-58 C09 (50)	96	96	215	**96**	0	1	1	4	0	0	0	**90**	93.8
Muenster Spider (51)	507	507	507	**507**	3	1	0	1	0	0	0	**502**	99.0
PHOBIA EXPOSURE (52)	20	20	20	**20**	1	1	0	0	0	0	0	**19**	95.0
PNC (53, 54)	945	854	854	**717**	4	5	4	6	43	4	0	**651**	90.8
Protect-AD (55)	57	57	57	**57**	1	0	0	0	0	0	0	**56**	98.2
RepSpi (56)	38	38	38	**38**	0	0	0	0	0	0	0	**38**	100.0
SDAN (57, 58)	119	119	119	**119**	0	0	0	0	0	0	0	**119**	100.0
SHIP (59)	995	977	995	**977**	80	0	0	55	0	3	238	**649**	66.4
SMARTSCAN (60)	93	93	95	**93**	0	0	0	0	0	0	0	**93**	100.0
SPIN	14	14	14	**14**[b]	0	2	0	0	0	0	0	**0**[b]	0.0
SPIN NF (61)	19	19	19	**19**	11	11	0	1	0	0	0	**7**	36.8
Teneriffa (62)	77	77	78	**77**	0	0	0	4	0	0	0	**73**	94.8
Uppsala (63)	47	47	47	**47**	0	0	0	1	0	0	0	**46**	97.8
Vanderbilt (64, 65)	19	19	18	**18**	0	0	0	0	0	0	0	**18**	100.0
Wuerzburg SFBTRR-58 C09 (50)	87	87	87	**87**	0	0	0	0	0	0	0	**87**	100.0
Wuerzburg Spider (66)	36	36	36	**36**	4	5	3	3	0	0	0	**28**	77.8
Wuerzburg Spider II	25	25	25	**25**	2	1	0	0	0	0	0	**23**	92.0
Wuerzburg Spider III	16	16	0	**0**	0	0	0	0	0	0	0	**0**	0.0

Total	**5 330**	**5 221**	**7 280**	**5 053**	**109**	**28**	**23**	**99**	**43**	**9**	**343**	**4 443**	**87.9**

initial datasets cortical / subcortical / covariate file: Datasets (subjects) were counted regardless of whether raw MRI data or the results of the Freesurfer preprocessing done on site were contributed.

[a]Includes a group of social phobia subjects without specific phobia that were thus not included in any group here.

[b]Not considered further due to <10 initial specific phobia datasets.

BHRCS: Brazilian High Risk Cohort Study; BION-SP: Bender Institute of Neuroimaging; COMIC: COMIC Research / Leeds and York Partnership NHS Foundation Trust; Dresden CRC940C5: DFG Collaborative Research Centre 940, project C5; Marburg FOR2107 MR: DFG-Research Group 2107 Marburg site; Muenster FOR2107 MS: DFG-Research Group 2107 Muenster site; Muenster SFBTRR-58 C09: DFG Collaborative Research Centre Transregio 58, project C09, Muenster 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; Wuerzburg SFBTRR-58 C09: DFG Collaborative Research Centre Transregio 58, project C09, Wuerzburg site.

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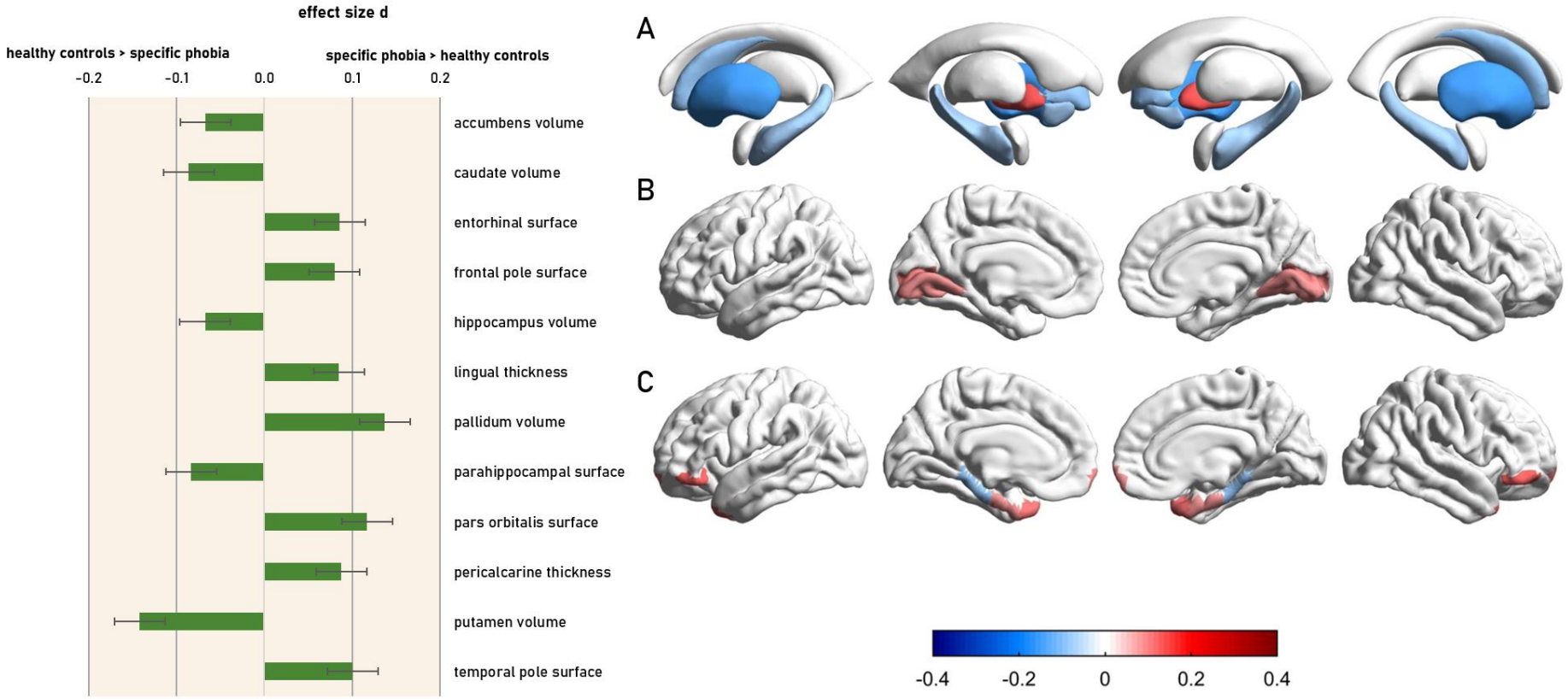
Table 2. Sociodemographic characteristics of the sample used for the main analysis.

							all						specific phobia						healthy controls				
		n					sex	age			education		sex	age			education		sex	age			education	
		subtype																						
Study	specific phobia (formal diagnosis)	Animal	BII	Other / un-known	healthy controls	**total**	% female	m	sd	range	m	sd	% female	m	sd	range	m	sd	% female	m	sd	range	m	sd
Barcelona	34 (34)	16	18	0	18	**52**	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
BHRCS	76 (28)	76	0	0	422	**498**	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
BION-SP	15 (15)	15	0	0	10	**25**	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
Bochum	15 (15)	0	15	0	0	**15**	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
COMIC	12 (12)	12	0	0	0	**12**	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
Czuwaj	25 (0)	12	13	0	11	**36**	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
Dresden CRC940C5	97 (97)	96	0	0	81	**178**	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
Dresden Phobia Subtypes	59 (22)	33	26	0	30	**89**	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
Graz	41 (41)	0	41	0	39	**80**	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
Graz II	25 (25)	0	25	0	27	**55**	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
Greifswald	20 (0)	20	0	0	24	**44**	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
Jena	14 (14)	14	0	0	15	**29**	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
Marburg FOR2107 MR	16 (16)	8	0	8	515	**531**	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

Muenster FOR2107 MS	27 (27)	5	3	19	243	**270**	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
Muenster SFBTRR-58 C09	90 (90)	85	0	5	0	**90**	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
Muenster Dental	18 (0)	0	18	0	19	**37**	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
Muenster Spider	29 (29)	29	0	0	473	**502**	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
PHOBIA EXPOSURE	19 (19)	19	0	0	0	**19**	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
PNC	319 (319)	0	0	319	332	**650**	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
Protect-AD	56 (56)	6	8	42	0	**56**	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
RepSpi	18 (0)	18	0	0	20	**38**	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
SDAN	47 (47)	0	0	47	72	**119**	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
SHIP	130 (125)	29	15	81	519	**649**	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
SMARTSCAN	46 (46)	46	0	0	47	**93**	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
SPIN NF	7 (7)	7	0	0	0	**7**	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
Teneriffa	34 (34)	34	0	0	39	**73**	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
Uppsala	46 (0)	46	0	0	0	**47**	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
Vanderbilt	9 (9)	2	0	7	9	**18**	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
Wuerzburg SFBTRR-58 C09	87 (87)	87	0	0	0	**87**	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
Wuerzburg Spider	11 (0)	11	0	0	16	**27**	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

Wuerzburg Spider II	13 (0)	13	0	0	10	**23**	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
Total	1 452(1 213)	739	182	528	2 991	4 443	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

BHRCS: Brazilian High Risk Cohort Study; BION-SP: Bender Institute of Neuroimaging; COMIC: COMIC Research / Leeds and York Partnership NHS Foundation Trust; Dresden CRC940C5: DFG Collaborative Research Centre 940, project C5; Marburg FOR2107 MR: DFG-Research Group 2107 Marburg site; Muenster FOR2107 MS: DFG-Research Group 2107 Muenster site; Muenster SFBTRR-58 C09: DFG Collaborative Research Centre Transregio 58, project C09, Muenster 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; Wuerzburg SFBTRR-58 C09: DFG Collaborative Research Centre Transregio 58, project C09, Wuerzburg site.



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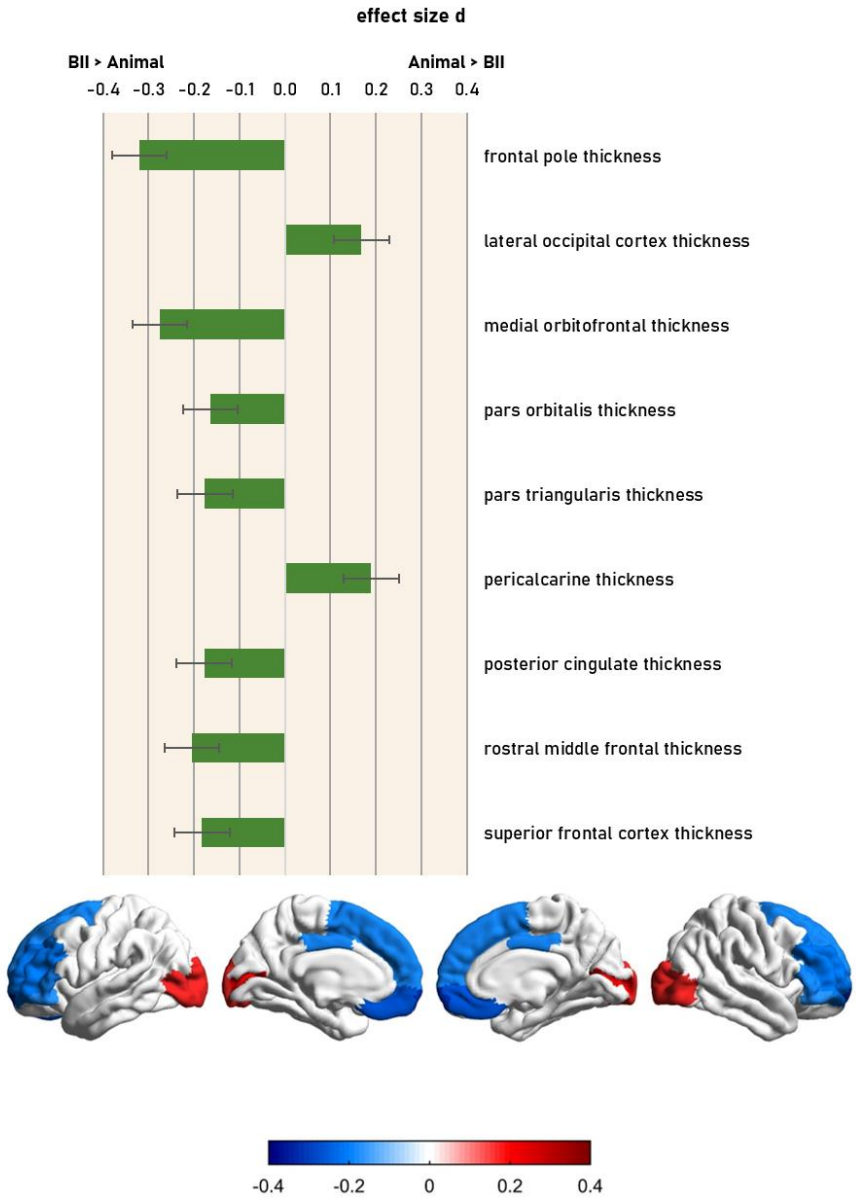
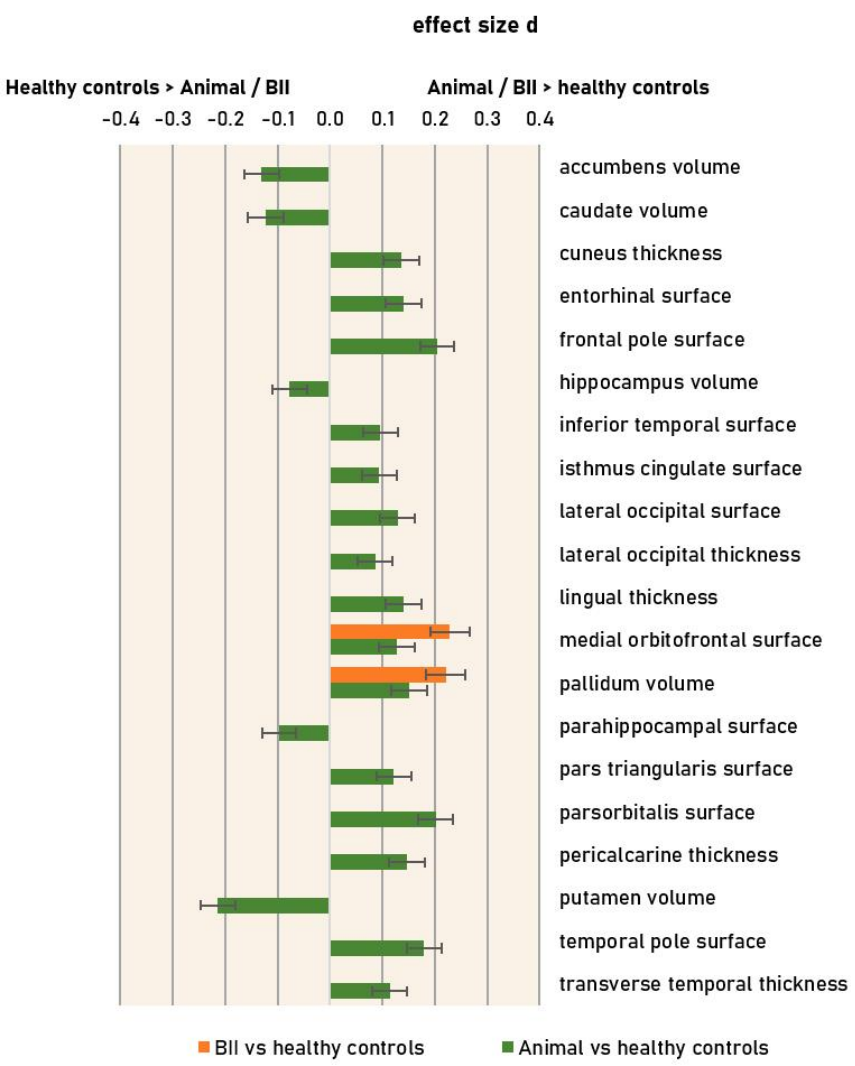
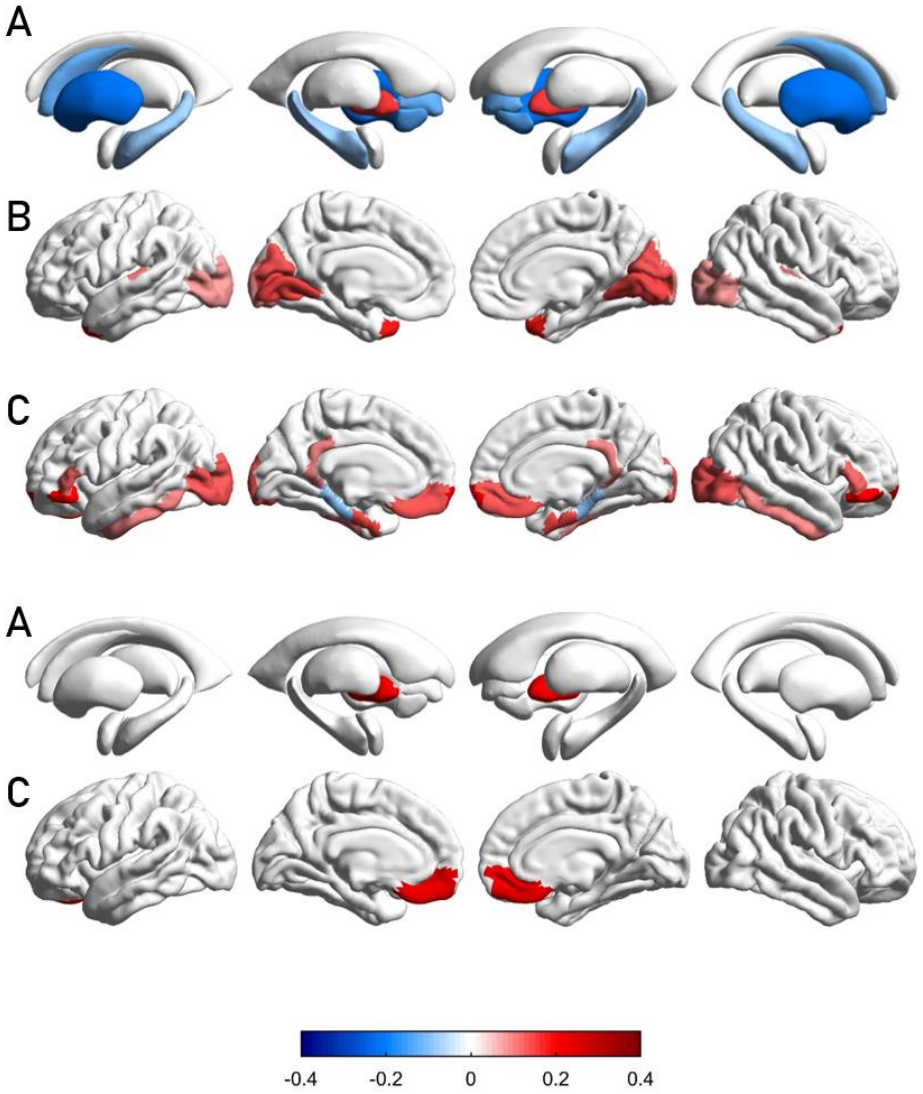

effect size d
BII > Animal
Animal > BII
-0.4 -0.3 -0.2 -0.1 0.0 0.1 0.2 0.3 0.4
frontal pole thickness
lateral occipital cortex thickness
medial orbitofrontal thickness
pars orbitalis thickness
pars triangularis thickness
pericalcarine thickness
posterior cingulate thickness
rostral middle frontal thickness
superior frontal cortex thickness
-0.4 -0.2 0 0.2 0.4

718


effect size d
Healthy controls > Animal / BII
Animal / BII > healthy controls
-0.4 -0.3 -0.2 -0.1 0.0 0.1 0.2 0.3 0.4
accumbens volume
caudate volume
cuneus thickness
entorhinal surface
frontal pole surface
hippocampus volume
inferior temporal surface
isthmus cingulate surface
lateral occipital surface
lateral occipital thickness
lingual thickness
medial orbitofrontal surface
pallidum volume
parahippocampal surface
pars triangularis surface
parsorbitalis surface
pericalcarine thickness
putamen volume
temporal pole surface
transverse temporal thickness
BII vs healthy controls
Animal vs healthy controls


A
B
C
A
C
-0.4
-0.2
0
0.2
0.4

719