Volume of subcortical brain regions in social anxiety disorder: mega-analytic results from 37 samples in the ENIGMA-Anxiety Working Group

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ARTICLE

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Volume of subcortical brain regions in social anxiety disorder: mega-analytic results from 37 samples in the ENIGMA-Anxiety Working Group

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There is limited convergence in neuroimaging investigations into volumes of subcortical brain regions in social anxiety disorder (SAD). The inconsistent findings may arise from variations in methodological approaches across studies, including sample selection based on age and clinical characteristics. The ENIGMA-Anxiety Working Group initiated a global mega-analysis to determine whether differences in subcortical volumes can be detected in adults and adolescents with SAD relative to healthy controls. Volumetric data from 37 international samples with 1115 SAD patients and 2775 controls were obtained from ENIGMA-standardized protocols for image segmentation and quality assurance. Linear mixed-effects analyses were adjusted for comparisons across seven subcortical regions in each hemisphere using family-wise error (FWE)-correction. Mixed-effects *d* effect sizes were calculated. In the full sample, SAD patients showed smaller bilateral putamen volume than controls (left: $d = -0.077$, $p_{FWE} = 0.037$; right: $d = -0.104$, $p_{FWE} = 0.001$), and a significant interaction between SAD and age was found for the left putamen ($r = -0.034$, $p_{FWE} = 0.045$). Smaller bilateral putamen volumes (left: $d = -0.141$, $p_{FWE} < 0.001$; right: $d = -0.158$, $p_{FWE} < 0.001$) and larger bilateral pallidum volumes (left: $d = 0.129$, $p_{FWE} = 0.006$; right: $d = 0.099$, $p_{FWE} = 0.046$) were detected in adult SAD patients relative to controls, but no volumetric differences were apparent in adolescent SAD patients relative to controls. Comorbid anxiety disorders and age of SAD onset were additional determinants of SAD-related volumetric differences in subcortical regions. To conclude, subtle volumetric alterations in subcortical regions in SAD were detected. Heterogeneity in age and clinical characteristics may partly explain inconsistencies in previous findings. The association between alterations in subcortical volumes and SAD illness progression deserves further investigation, especially from adolescence into adulthood.

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INTRODUCTION

Social anxiety disorder (SAD) is characterized by an intense, disproportionate, and invalidating fear of negative evaluation as may occur in social and performance contexts, leading to severe distress and reduced quality of life [1–3]. The condition has a global prevalence of 4–7% ([4, 5]; also see [6]), typically starts in early adolescence [7, 8] and frequently persists in adulthood [4, 6]. Many affected individuals develop comorbid psychopathology in

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addition to SAD, most notably other anxiety and depressive disorders [6, 9]. Neurobiological models of SAD have emphasized the role of subcortical fear circuitry in social approach-avoidance conflicts and the perception of threat, encompassing the amygdala and hippocampus, and in addition the striatum [10–13]. Our understanding of the neurobiology of SAD is incomplete, and conflicting findings regarding morphological differences in subcortical brain regions pose one of the major unknowns[1].

Smaller-scale empirical studies, typically including <50 SAD patients, have repeatedly reported volumetric differences relative to controls in the amygdala and hippocampus [14–19]. Smaller volumes tend to be reported more frequently in the right hemisphere ([16, 17]; trends in [20, 21]), however, the direction of effect overall is highly inconsistent [10, 22]. A more recent voxel-based morphometry mega-analysis investigating amygdala, hippocampus, and striatum regions of interest (ROIs) in 174 adult SAD patients [23] and a retrospective coordinate-based meta-analysis in 470 adolescent and adult SAD patients ([24]; excluding ROI studies) did not identify volumetric differences in the hippocampus and amygdala. Instead, both studies implicated the putamen, though different subregions and direction of effects. The mega-analysis [23] found a larger gray matter volume in the right dorsal putamen, whereas the meta-analysis [24] reported a smaller left ventral putamen volume in SAD patients. Finally, there is evidence for involvement of the thalamus in SAD [16, 24, 25]. In summary, inconsistent volumetric differences in subcortical regions have been observed in SAD. The findings are difficult to synthesize because of methodological heterogeneity, for example, related to ROI definition and sample selection criteria.

Volumetric differences in subcortical brain regions might be more pronounced in specific subgroups of SAD patients, for example in individuals that are medication-free (smaller thalamus: 24), had an earlier onset of SAD (smaller thalamus, amygdala: 16) and higher symptom severity (smaller amygdala: 14; larger putamen: 23). These isolated findings are in need of replication and point toward interesting open questions. For example, it remains unclear to what extent psychiatric comorbidities impact subcortical volumetric alterations in SAD [26]. Furthermore, while most patients develop the condition in adolescence, it is presently unclear whether volumetric differences in subcortical circuitry already manifest in adolescents with SAD [27]. The largest study to date [28] identified a smaller right hippocampal volume in 75 young adolescents with an anxiety disorder (mean age: 12 years; age range: 8–18 years). However, in post-hoc analyses this difference was attributed to generalized anxiety disorder (GAD) and not SAD diagnosis. No difference in amygdala volume was detected in these young adolescents [28], and neither in a study of slightly older adolescents with SAD ([29]; mean age: 16 years; age range: 15–17 years). The above-mentioned large, aggregated studies did not include adolescents at all [24] or included an insufficient number of adolescent samples to allow a dedicated sub-analysis [25]. While it is plausible that age and clinical characteristics (i.e., psychiatric comorbidity, medication use, age of onset, symptom severity) are of importance for SAD-related volumetric alterations in subcortical regions, this is to be confirmed in well-powered analyses.

The ENIGMA-Anxiety Working Group (overview: [30]; preliminary findings: [31]) initiated a worldwide effort to perform the largest coordinated multi-site analysis on subcortical volumes in SAD to date, including data on 1115 SAD and 2775 healthy control (HC) participants. In the present investigation, our principal aim was to determine whether alterations in subcortical volumes can be detected in SAD relative to HC participants, using a standardized protocol to harmonize image processing across sites. To optimally address variability within and between samples, volumetric data were pooled in a mega-analysis of individual participant data (in line with: [32, 33]). The analysis in the aggregated sample was supplemented with a sub-analysis in adolescent participants, thus presenting the first large mega-analysis of subcortical volumes in adolescents with SAD, as well as a sub-analysis in adult participants. Furthermore, SAD-related volumetric differences were examined in relation to psychiatric comorbidity, medication use, age of onset and symptom severity.

[1]While regions of the frontal cortex also feature in neurobiological models of SAD, the focus of the present investigation is exclusively on subcortical brain regions.

MATERIALS AND METHODS

Samples

Volumetric data from 1115 SAD and 2775 HC participants obtained from 37 samples originating from ten countries across five continents, were available for mega-analysis (Table 1). Lifetime or current SAD was established by diagnostic interview (Table 1). Two samples did not assess current SAD (PNC, SHIP). In the other 35 samples, only 2.5% of the total included SAD patients met criteria for lifetime SAD but not current SAD. Exclusion criteria for SAD patients were comorbid schizophrenia (or schizophrenia spectrum disorder), bipolar disorder, and autism spectrum disorder. Exclusion criteria for HCs were lifetime major psychiatric diagnoses and psychotropic medication use at the time of scan, when this information was available. Additional study-specific exclusion criteria applied, as reflected in the sample characteristics (Table 2; Supplemental Table 1). Studies with multiple scan sites (BHRCS, FOR_2107, NESDA) were treated as separate samples per scan site. Individual studies were approved by relevant local ethical review boards and written informed consent was obtained from participants prior to data collection.

Image acquisition and processing

T1-weighted brain magnetic resonance imaging (MRI) scans were acquired at each scan site (1.5 T or 3.0 T). Details regarding image acquisition and software versions are provided in Supplemental Table 2. MRI scans were processed using the automated and validated segmentation software package FreeSurfer [34], in accordance with the ENIGMA-standardized protocol for brain segmentation and quality assurance (http://enigma.ini.usc.edu/protocols/imaging-protocols/). The segmentations of 14 subcortical regions (for each hemisphere: thalamus, amygdala, hippocampus, putamen, pallidum, nucleus accumbens, and caudate; Fig. 1) and of the whole brain were visually inspected for accuracy. The distribution and variance of volumes in the total sample and in SAD and HC subgroups were visually inspected to identify potential outliers. Segmentations that did not pass quality control were excluded from analysis (approach detailed in Supplemental Note 1).

Linear mixed-effects models

A series of linear models were fitted with volume per subcortical region as outcome variable and SAD diagnosis (dichotomous factor) or symptom severity (continuous variable) as main regressor. The following covariates were used: sex, age, age^2, sex-by-age, sex-by-age^2 and total intracranial volume (ICV). Age was centred throughout. Mixed-effects *d* effect sizes were calculated from the *t*-values for diagnostic factor, and mixed-effects *r* estimates were calculated for relevant interaction and continuous variables of interest (Supplemental Note 1). These are similarly scaled as Cohen's *d* estimates and *r* estimates, but include a correction for non-independence in the aggregated dataset [35]. Throughout the analyses, samples were only included for between-group contrasts when at least one observation per group was available for each of the subcortical regions. The threshold for significance was set at family-wise error (FWE)-corrected $p < 0.05$, adjusting for 14 subcortical regions ($p_{unc} < 0.00357$) in all analyses.

First, the full SAD sample was compared to all HCs. In sensitivity analyses, SAD patients were excluded for comorbid lifetime obsessive-compulsive disorder (OCD; excluded: comorbid OCD: $n = 29$; OCD not assessed: $n = 178$), lifetime post-traumatic stress disorder (PTSD; excluded: comorbid PTSD: $n = 66$; PTSD not assessed: $n = 155$), or were excluded when current SAD criteria were not met (lifetime but not current SAD: $n = 21$; current SAD not assessed: $n = 184$). Next, SAD *diagnosis-by-sex, diagnosis-by-age* and *diagnosis-by-age*^{2} interactions were tested in the full sample. SAD vs HC comparisons were also made according to *age group* cf.

Table 1. Demographic information for samples included in the mega-analysis of subcortical volumes in social anxiety disorder patients vs healthy controls.

Sample		Country	Diagnostic interview	Social anxiety disorder (SAD)				Healthy Controls (HC)			
				N	Sex % Female	Age mean ± sd	Adults % >21 yrs	*N*	Sex % Female	Age mean ± sd	Adults % >21 yrs
1	BCM	US	SCID	59	33.9	30.1 ± 11.7	78.0	75	48.0	28.8 ± 9.7	81.3
2	BHRC_RS	BR	DAWBA	15	46.7	13.5 ± 1.9	0.0	22	54.5	13.2 ± 2.1	0.0
3	BHRC_SP	BR	DAWBA	12	41.7	12.8 ± 1.7	0.0	24	37.5	12.6 ± 1.6	0.0
4	Boystown	US	Other	50	74.0	15.4 ± 1.7	0.0	44	59.1	14.8 ± 1.8	0.0
5	Columbia_SAD	US	Other	17	64.7	29.1 ± 8.9	88.2	17	58.8	31.4 ± 10.8	88.2
6	Columbia_SPP	US	SCID	16	81.3	34.6 ± 8.3	100.0	18	44.4	31.6 ± 8.2	100.0
7	DCCN	NL	MINI	23	56.5	33.2 ± 11.7	82.6	24	66.7	32.1 ± 10.8	83.3
8	DelMar	ES	Other	63	66.7	24.0 ± 6.1	55.6	99	56.6	28.3 ± 9.6	73.7
9	Dresden	DE	CIDI	20	60.0	24.6 ± 5.7	60.0	21	61.9	25.8 ± 5.7	90.5
10	FOR2107_MR	DE	SCID	29	69.0	30.4 ± 9.2	82.8	411	62.5	34.8 ± 12.8	92.5
11	FOR2107_MS	DE	SCID	27	63.0	38.8 ± 13.3	85.2	238	64.7	28.1 ± 10.1	82.8
12	Fortuene	DE	SCID	12	50.0	23.3 ± 3.4	66.7	14	50.0	25.3 ± 2.1	92.9
13	HMRRC	CN	SCID	19	31.6	21.6 ± 3.8	36.8	20	30.0	21.5 ± 3.8	35.0
14	Houston	US	SCID	34	44.1	29.2 ± 15.2	58.8	34	44.1	29.1 ± 15.2	58.8
15	Istanbul	TR	SCID	30	26.7	32.6 ± 6.5	100.0	21	38.1	30.9 ± 6.0	100.0
16	LFLSAD	NL	MINI	10	70.0	45.6 ± 4.5	100.0	11	36.4	47.1 ± 12.3	90.9
17	Louvain	BE	MINI	23	100.0	22.7 ± 3.1	73.9	23	100.0	22.7 ± 3.9	65.2
18	LUMC	NL	MINI	20	45.0	28.9 ± 7.9	80.0	19	42.1	27.7 ± 8.0	89.5
19	M_Pack	DE	SCID	45	62.2	27.5 ± 7.0	91.1	46	63.0	26.7 ± 4.8	97.8
20	MRC_SU	ZA	SCID	11	72.7	32.1 ± 8.3	81.8	11	63.6	32.2 ± 8.9	90.9
21	MRC_UCT	ZA	SCID	11	54.5	28.5 ± 7.8	81.8	11	36.4	28.9 ± 7.3	72.7
22	MSAD	DE	SCID	19	42.1	36.1 ± 14.6	89.5	22	27.3	31.8 ± 9.0	86.4
23	NESDA_Ams	NL	CIDI	35	54.3	37.9 ± 9.9	97.1	21	61.9	39.8 ± 9.2	100.0
24	NESDA_Lei	NL	CIDI	33	69.7	37.8 ± 10.1	93.9	27	74.1	40.3 ± 9.6	96.3
25	NESDA_Gro	NL	CIDI	34	73.5	37.7 ± 9.6	97.1	11	54.5	44.6 ± 9.7	100.0
26	PNC[a]	US	Other	155	61.3	14.7 ± 3.4	0.0	398	48.0	14.1 ± 4.0	1.0
27	SDAN	US	SCID&KSADS	30	73.3	12.5 ± 3.3	0.0	22	50.0	12.1 ± 2.3	0.0
28	SHIP[a]	DE	CIDI	29	62.1	52.3 ± 10.8	100.0	397	46.6	53.6 ± 10.9	100.0
29	SP_Munster	DE	SCID	67	79.1	32.9 ± 11.0	91.0	490	55.7	37.3 ± 11.9	92.2
30	TIP	DE	SCID	14	64.3	23.9 ± 4.2	64.3	23	91.3	23.7 ± 8.1	47.8
31	UCSD_Ball	US	SCID	15	66.7	21.2 ± 2.2	46.7	18	66.7	18.6 ± 0.8	0.0
32	UCSD_Sapient	US	MINI	25	60.0	26.1 ± 8.7	64.0	25	64.0	28.0 ± 8.2	80.0
33	UIC	US	SCID	12	75.0	27.9 ± 7.2	91.7	11	63.6	32.7 ± 11.2	90.9
34	UME_I	SE	SCID	26	84.6	32.3 ± 9.6	88.5	23	69.6	32.3 ± 10.7	87.0
35	UME_II	SE	MINI&SCID	46	63.0	30.7 ± 8.3	89.1	42	57.1	31.9 ± 9.5	90.5
36	Vanderbilt	US	SCID	10	60.0	22.1 ± 2.0	60.0	14	64.3	23.0 ± 1.7	71.4
37	Washington	US	KSADS	19	52.6	10.2 ± 1.5	0.0	28	50.0	9.9 ± 1.2	0.0
Total across all samples				1115	61.5	26.9 ± 12.3	60.5	2775	55.2	31.9 ± 15.6	71.6

SCID Structured Clinical Interview for DSM-IV disorders, *DAWBA* Development and Well-Being Behavior Assessment, *MINI* Mini-International Neuropsychiatric Interview, *CIDI* Composite Interview Diagnostic Instrument, *KSADS* Kiddie Schedule for Affective Disorders and Schizophrenia for school-age children, *sd* standard deviation, *yrs* years.

[a]The Philadelphia Neuroimaging Cohort (PNC) and Study of Health in Pomerania (SHIP) assessed lifetime but not current SAD diagnosis.

Table 2. Clinical characteristics for samples included in the mega-analysis (selectively reported for social anxiety disorder patients).

Sample		Lifetime comorbidity		Psychotropic medication[a]		Age of onset		LSAS	STAI-T	BDI-II
		% ANX	% MDD	% Any use	% SSRI/SNRI	Mean ± sd	% Early onset[b]	Mean ± sd	Mean ± sd	Mean ± sd
1	BCM	37.3	62.7	69.5	45.8	–[c]	–	–	–	–
2	BHRC_RS	40.0	46.7	13.3	6.7	–	26.7	–	–	–
3	BHRC_SP	41.7	25.0	0.0[d]	0.0	–	33.3	–	–	–
4	Boystown	58.0	38.0	52.0	28.0	–	6.0	67.6 ± 22.7	–	–
5	Columbia_SAD	17.6	35.3	0.0	0.0	–	–	81.4 ± 15.6	–	–
6	Columbia_SPP	31.3	31.3	18.8	12.5	10.6 ± 6.0	68.8	–	39.1 ± 9.1	–
7	DCCN	21.7	17.4	0.0	0.0	–	–	66.9 ± 20.3	–	13.0 ± 7.6
8	DelMar	0.0	0.0	0.0	0.0	–	–	83.4 ± 17.2	40.4 ± 5.6	–
9	Dresden	25.0	35.0	0.0	0.0	11.8 ± 6.1	25.0	58.1 ± 30.2	49.0 ± 11.2	12.4 ± 7.5
10	FOR2107_MR	48.3	100.0	82.8	69.0	–	–	–	62.0 ± 7.4	22.8 ± 9.4
11	FOR2107_MS	37.0	100.0	66.7	66.7	–	–	–	57.7 ± 9.7	21.9 ± 11.0
12	Fortuene	8.3	25.0	0.0	0.0	–	–	62.9 ± 17.7	48.2 ± 7.9	10.4 ± 5.7
13	HMRRC	0.0	0.0	0.0	0.0	17.2 ± 5.9	21.1	52.0 ± 14.0	–	–
14	Houston	41.2	100.0	11.8	–	10.1 ± 5.2	26.5	–	–	26.1 ± 15.2
15	Istanbul	6.7	0.0	0.0	0.0	–	–	73.1 ± 17.8	–	–
16	LFLSAD	40.0	50.0	10.0	10.0	6.0 ± 2.7	100.0	65.9 ± 23.0	43.8 ± 9.1	13.6 ± 10.5
17	Louvain	0.0	0.0	0.0	0.0	–	–	74.2 ± 11.1	51.0 ± 9.3	15.7 ± 8.4
18	LUMC	0.0	25.0	10.0	10.0	–	–	85.7 ± 13.5	–	19.1 ± 9.1
19	MPack	17.8	15.6	15.6	11.1	–	–	66.6 ± 17.7	52.5 ± 9.5	14.4 ± 11.4
20	MRC_SU	0.0	0.0	0.0	0.0	16.4 ± 9.0	27.3	85.3 ± 24.2	53.3 ± 10.7	15.5 ± 11.6
21	MRC_UCT	9.1	0.0	9.1	–	14.6 ± 5.7	27.3	78.8 ± 30.8	–	–
22	MSAD	26.3	31.6	0.0	0.0	–	–	66.8 ± 15.0	–	13.6 ± 9.6
23	NESDA_Ams	74.3	80.0	45.7	34.3	12.9 ± 6.3	54.3	–	–	–
24	NESDA_Lei	84.8	81.8	48.5	33.3	13.6 ± 8.9	57.6	–	–	–
25	NESDA_Gro	85.3	82.4	55.9	38.2	20.2 ± 12.6	32.4	–	–	–
26	PNC	53.5	15.5	12.3	3.2	–	25.2	–	34.4 ± 9.2	–
27	SDAN	80.0	3.3	0.0	0.0	–	50.0	–	35.8 ± 10.2	–
28	SHIP	65.5	62.1	41.4	13.8	21.6 ± 17.1	51.7	–	–	15.8 ± 11.5
29	SP_Munster	16.4	52.2	25.4	25.4	17.6 ± 12.3	28.4	60.5 ± 19.5	55.7 ± 11.2	17.2 ± 10.9
30	TIP	0.0	78.6	35.7	35.7	14.0 ± 6.9	28.6	66.0 ± 22.9	52.8 ± 12.7	10.1 ± 8.7
31	UCSD_Ball	6.7	40.0	0.0	0.0	–	–	57.9 ± 19.4	57.5 ± 13.6	20.1 ± 12.4
32	UCSD_Sapient	0.0	0.0	0.0	0.0	–	–	–	54.7 ± 8.4	14.6 ± 10.1
33	UIC	50.0	8.3	0.0	0.0	13.9 ± 6.4	41.7	82.7 ± 18.6	55.2 ± 11.0	16.8 ± 10.7
34	UME_I	–	0.0	34.6	30.8	15.9 ± 6.0	19.2	76.3 ± 18.7	–	–
35	UME_II	26.1	65.2	8.7	8.7	13.8 ± 4.7	28.3	78.0 ± 19.0	43.4 ± 9.1	–
36	Vanderbilt	80.0	20.0	0.0	0.0	14.0 ± 4.2	10.0	–	47.7 ± 10.6	12.6 ± 11.1
37	Washington	73.7	15.8	5.3	0.0	5.4 ± 2.3	100.0	–	–	–
Total across all samples		35.9	37.5	22.2	15.2	14.9 ± 9.8	21.5	71.2 ± 21.1	46.4 ± 13.3	16.5 ± 10.9

LSAS Liebowitz Social Anxiety Scale, *STAI-T* State-Trait Anxiety Inventory-Trait, *BDI-II* Beck Depression Inventory 2nd Edition, *ANX* Any comorbid anxiety disorder, *MDD* Major Depressive Disorder, *SSRI* Selective Serotonin Reuptake Inhibitor, *SNRI* Serotonin-Norepinephrine Reuptake Inhibitor, *sd* standard deviation.
[a]Medication use at time of scan (% in full sample).
[b]Defined as social anxiety disorder onset prior to 13 years of age.
[c]Information not recorded in this sample (–).
[d]Not included in this sample ($n = 0$).

[36]: child/adolescent SAD vs HC (range: 8–21 years; hereafter abbreviated to adolescent SAD) and adult SAD vs HC (range: 22–69 years).

Next, clinical characteristics of SAD were investigated in relation to subcortical volumes. The following characteristics were used to define SAD subgroups: *comorbid anxiety disorders* (lifetime GAD, panic disorder, agoraphobia, specific phobia, or any other anxiety diagnoses that were assessed), *psychotropic medication use* at the time of scan, and *early onset of disease* (<13 years according to median onset; see Supplementary Note 1). SAD patients with and without these characteristics were separately contrasted with HCs. As clinical characteristics differed

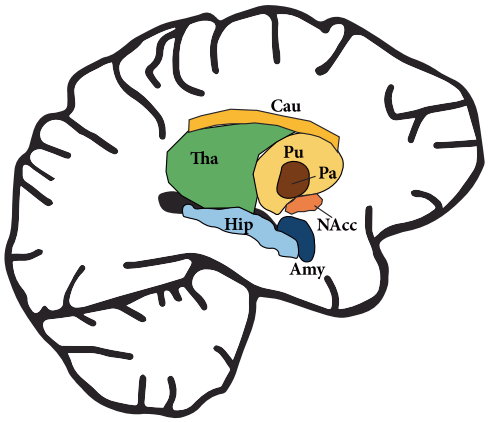

Fig. 1 Schematic overview of the seven subcortical brain regions segmented for each hemisphere. *THA = thalamus, HIP = hippocampus, AMY = amygdala, CAU = caudate, PU = putamen, PA = pallidum, NACC = (nucleus) accumbens.*

considerably between adult and adolescent SAD patients, sensitivity analyses were conducted in adult and adolescent age groups when appropriate (≥5 samples with total ≥100 adult or adolescent SAD patients per clinical subgroup; Table 3). For completeness, SAD patients with and without the relevant clinical characteristics were also contrasted directly in supplemental subgroup analyses.

Additional supplemental subgroup analyses (SAD relative to HCs) were conducted for SAD patients with and without lifetime major depressive disorder (MDD) comorbidity, and medication use restricted to selective serotonin reuptake inhibitors (SSRI) and serotonin-noradrenaline reuptake inhibitors (SNRI), because of their overlapping mechanisms of action. Finally, associations between subcortical volumes and *symptom severity* were examined in SAD patients. Severity of social anxiety was measured with the Liebowitz Social Anxiety Scale (LSAS total score [37];) in 21 samples (total $n = 523$), trait anxiety with the State-Trait Anxiety Inventory (STAI trait score [38];) in 19 samples (total $n = 539$), and depressive symptoms with the Beck Depression Inventory second edition (BDI-II total score [39];) in 19 samples (total $n = 409$).

Selection mega-analytic approach

All linear mixed-effects models were fitted with a random-intercept to account for data clustering within samples. Both models with a random slope for diagnosis per sample (complex model) and without random slope (reference model) were fitted, and fit was compared using the Likelihood Ratio Test (LRT; cf. 33, $p < 0.05$ indicates improved model fit in complex relative to reference model). The mega-analytic model with the best model fit for the majority of subcortical regions was selected, based on the full sample. All mega-analysis models were fitted with restricted maximum likelihood (ReML [40];) in R version 3.6.3 (nlme package) and mixed-effects *d* and *r* effect sizes were computed (Supplemental Note 1).

RESULTS

Model fit

Model fit comparisons were conducted on data from 37 samples with a total of 1115 SAD patients and 2775 HCs (full aggregated sample). The inclusion rate of volumetric observations after quality control was 97.7% across all subcortical regions. For 9/14 subcortical regions, the complex model with random intercept (scan site) and random slope (SAD diagnosis per scan site) did not show a significant improvement in model fit compared to the random intercept (scan site) reference model (Supplemental Table 3). Hence, all subsequent analyses were conducted with the random intercept (scan site) model.

Subcortical brain volumes in social anxiety disorder relative to controls

An overview of findings from the main and subgroup analyses is provided in Table 3. SAD patients (full sample including current and lifetime SAD diagnoses) showed a smaller volume of the bilateral putamen (left putamen: mixed-effects $d = -0.077$, $p_{FWE} = 0.037$; right putamen: mixed-effects $d = -0.104$, $p_{FWE} = 0.001$) compared to HCs (Fig. 2). The effect sizes were robust in three sensitivity analyses, excluding SAD patients with comorbid OCD, comorbid PTSD, or no current SAD diagnosis (range in mixed-effects *d* for left putamen [−0.094, −0.074]; right putamen [−0.120, −0.108]), although the left putamen was no longer significant when restricting the analysis to current SAD vs HCs (mixed-effects $d = -0.074$, $p_{FWE} = 0.156$; Supplemental Table 4a, b).

Social anxiety disorder interactions with age and sex

In the full sample, a significant negative interaction between SAD diagnosis and age was found for the left putamen (mixed-effects $r = -0.034$, $p_{FWE} = 0.045$). Analyses by age group provided more insight into this negative interaction. The mega-analysis in adults revealed smaller volumes of the bilateral putamen (left putamen: mixed-effects $d = -0.141$, $p_{FWE} < 0.001$; right putamen: mixed-effects $d = -0.158$, $p_{FWE} < 0.001$) and larger volumes of the bilateral pallidum (left pallidum: mixed-effects $d = 0.129$, $p_{FWE} = 0.006$; right pallidum: mixed-effects $d = 0.099$, $p_{FWE} = 0.046$) in SAD patients compared to HCs. However, there were no significant differences between adolescents with SAD and adolescent HCs (Fig. 2; Supplemental Table 5a, b). Furthermore, there were no significant interactions between SAD and sex, nor between SAD and age^2 in the full sample (Supplemental Note 2).

Social anxiety disorder subgroups: comorbid anxiety disorders

SAD patients with a comorbid anxiety disorder showed a significantly smaller left amygdala volume (mixed-effects $d = -0.145$, $p_{FWE} = 0.017$) compared to HCs (Table 3). This volumetric difference did not reach significance when selectively including adult SAD patients with comorbid anxiety, despite a similar effect size (mixed-effects $d = -0.174$, $p_{FWE} = 0.077$); and neither in adolescent SAD patients with comorbid anxiety (mixed-effects $d = -0.110$, $p_{FWE} = 1.000$). Furthermore, smaller bilateral putamen volumes (left putamen: mixed-effects $d = -0.091$, $p_{FWE} = 0.046$; right putamen: mixed-effects $d = -0.097$, $p_{FWE} = 0.029$) were observed in SAD patients without a comorbid anxiety disorder compared to HCs (SAD subgroups compared to HCs presented in Supplemental Tables 6–8; contrasts between SAD subgroups in Supplemental Note 4). The smaller bilateral putamen finding replicated in adult SAD patients without comorbid anxiety, but not in adolescent SAD patients without comorbid anxiety. Of note, the volumetric differences observed for SAD subgroups with and without comorbid MDD were highly similar to the findings for comorbid anxiety disorders (Supplemental Note 3).

Social anxiety disorder subgroups: psychotropic medication use

No FWE-corrected significant differences in subcortical volumes were observed for SAD patients that used psychotropic medication at the time of scan compared to HCs. This also applied to the subset of SAD patients that specifically used SSRIs or SNRIs. SAD patients without psychotropic medication use at the time of scan showed a smaller right putamen volume (mixed-effects $d = -0.100$, $p_{FWE} = 0.007$) compared to HCs, and this difference was also significant when restricting the analysis to adult SAD patients without psychotropic medication (Table 3).

Social anxiety disorder subgroups: early and later onset

SAD patients with early onset demonstrated a smaller right hippocampus volume (mixed-effects $d = -0.194$, $p_{FWE} = 0.009$) compared to HCs. This finding was stronger in adult SAD with early onset (mixed-effects $d = -0.326$, $p_{FWE} < 0.001$). In SAD patients with later onset compared to HCs, smaller bilateral putamen (left putamen: mixed-effects $d = -0.336$, $p_{FWE} < 0.001$;

Table 3. Overview of mega-analytic results for main diagnostic group comparisons and clinical subgroup comparisons: sample sizes, effect sizes and *p* values.

Group Comparison	Sens.	Samples	SAD	HC	L-Putamen[a]		R-Putamen		L-Pallidum		R-Pallidum		L-Accumbens	
	Age	*N*	*N*	*N*	Mixeff.d	P_{FWE}[b,c]	Mixeff.d	P_{FWE}	Mixeff.d	P_{FWE}	Mixeff.d	P_{FWE}	Mixeff.d	P_{FWE}
SAD vs HC	–	37	1120	2781	**−0.077**	**0.037**	**−0.104**	**0.001**	0.058	0.572	0.065	0.186	ns	ns
SAD vs HC	Adu	30	668	1984	**−0.141**	**<0.001**	**−0.158**	**<0.001**	**0.129**	**0.006**	**0.099**	**0.046**	ns	ns
SAD vs HC	Ado	29	437	788	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
SAD ANX vs HC	–	29	404	2538	ns	ns	−0.105	0.185	ns	ns	ns	ns	ns	ns
SAD ANX vs HC	Adu	22	208	1811	ns	ns	**−0.198**	**0.010**	ns	ns	ns	ns	ns	ns
SAD ANX vs HC	Ado	15	191	661	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
SAD wo ANX vs HC	–	31	615	2613	**−0.091**	**0.046**	**−0.097**	**0.029**	0.105	0.051	0.081	0.184	ns	ns
SAD wo ANX vs HC	Adu	25	388	1868	**−0.146**	**0.003**	**−0.138**	**0.007**	**0.214**	**<0.001**	**0.141**	**0.006**	ns	ns
SAD wo ANX vs HC	Ado	25	216	736	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
SAD MED vs HC	–	20	246	2384	ns	ns	−0.141	0.216	ns	ns	ns	ns	ns	ns
SAD MED vs HC	Adu	15	170	1704	−0.158	0.441	−0.198	0.096	ns	ns	ns	ns	ns	ns
SAD MED vs HC	Ado[d]	11	75	645	–	–	–	–	–	–	–	–	–	–
SAD wo MED vs HC	–	37	850	2781	−0.081	0.058	**−0.100**	**0.007**	0.083	0.103	0.084	0.054	ns	ns
SAD wo MED vs HC	Adu	30	479	1984	**−0.154**	**<0.001**	**−0.157**	**<.0001**	**0.170**	**0.001**	**0.132**	**0.008**	ns	ns
SAD wo MED vs HC	Ado	27	356	771	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
SAD E-ONS vs HC	–	23	240	1729	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
SAD E-ONS vs HC	Adu	15	136	1071	**−0.229**	**0.040**	**−0.269**	**0.006**	ns	ns	ns	ns	ns	ns
SAD E-ONS vs HC	Ado[d]	12	98	621	–	–	–	–	–	–	–	–	–	–
SAD L-ONS vs HC	–	16	200	1174	**−0.336**	**<0.001**	**−0.309**	**<0.001**	**0.240**	**0.002**	**0.195**	**0.006**	**−0.171**	**0.024**
SAD L-ONS vs HC	Adu	16	174	1078	**−0.362**	**<0.001**	**−0.322**	**<0.001**	**0.260**	**0.001**	**0.199**	**0.006**	−0.157	0.083
SAD L-ONS vs HC	Ado[d]	7	22	38	–	–	–	–	–	–	–	–	–	–
Group comparison	**Sens.**	**Samples**	**SAD**	**HC**	**L-Amygdala[a]**		**R-Hippocampus**							
	Age	***N***	***N***	***N***	**Mixeff.d**	**P_{FWE}[b,c]**	**Mixeff.d**	**P_{FWE}**						
SAD vs HC	–	37	1120	2781	−0.068	0.308	−0.066	0.359						
SAD vs HC	Adu	30	668	1984	−0.076	0.674	ns	ns						
SAD vs HC	Ado	29	437	788	ns	ns	ns	ns						
SAD ANX vs HC	–	29	404	2538	**−0.145**	**0.017**	−0.120	0.137						
SAD ANX vs HC	Adu	22	208	1811	−0.174	0.077	−0.155	0.164						
SAD ANX vs HC	Ado	15	191	661	ns	ns	ns	ns						
SAD wo ANX vs HC	–	31	615	2613	ns	ns	ns	ns						
SAD wo ANX vs HC	Adu	25	388	1868	ns	ns	ns	ns						
SAD wo ANX vs HC	Ado	25	216	736	ns	ns	ns	ns						
SAD MED vs HC	–	20	246	2384	ns	ns	−0.143	0.282						
SAD MED vs HC	Adu	15	170	1704	ns	ns	ns	ns						
SAD MED vs HC	Ado[d]	11	75	645	–	–	–	–						
SAD wo MED vs HC	–	37	850	2781	−0.068	0.523	ns	ns						

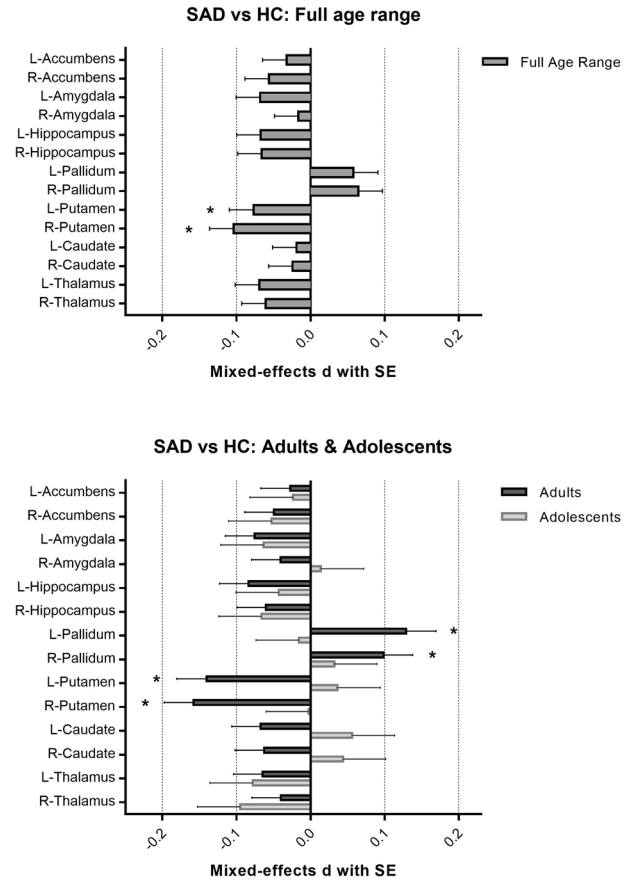

Fig. 2 Mixed-effects d effect size and Standard Error (SE) for differences in subcortical brain volume between social anxiety disorder (SAD) and healthy control (HC) participants, obtained in mega-analyses that were adjusted for sex, age, age^2, sex-by-age, sex-by-age^2 and total ICV. *Top panel*: Full age range. *Bottom panel*: Stratified according to adult and adolescent age group. *$p < 0.05$ after family-wise error correction for multiple comparisons.

right putamen: mixed-effects $d = -0.309$, $p_{FWE} < 0.001$) and left nucleus accumbens (mixed-effects $d = -0.171$, $p_{FWE} = 0.024$) volumes were found. In addition, larger bilateral pallidum volumes (left pallidum: mixed-effects $d = 0.240$, $p_{FWE} = 0.002$; right putamen: mixed-effects $d = 0.195$, $p_{FWE} = 0.006$) were observed. Most findings for later-onset SAD replicated in the adult subgroup (left putamen: mixed-effects $d = -0.362$, $p_{FWE} < 0.001$; right putamen: mixed-effects $d = -0.322$, $p_{FWE} < 0.001$; left pallidum: mixed-effects $d = 0.260$, $p_{FWE} = 0.001$; right pallidum: mixed-effects $d = 0.199$, $p_{FWE} = 0.006$). However, significance for the left nucleus accumbens was lost (Table 3).

Severity of social anxiety, trait anxiety and depressive symptoms

No significant associations were detected between subcortical volumes and the severity of social anxiety, trait anxiety, or depressive symptoms in SAD patients after FWE-correction for multiple comparisons (associations at $p_{unc} < 0.05$ presented in Supplemental Note 5).

DISCUSSION

In this study, the ENIGMA-Anxiety Working Group investigated differences in volume of subcortical brain regions between SAD patients and HCs, including 37 samples from research sites worldwide. We found evidence for subtle subcortical volumetric

Table 3. continued

Group comparison	Sens.	Samples	SAD	HC	L-Amygdala[a]		R-Hippocampus	
	Age	N	N	N	Mixeff.d	P_{FWE}[b,c]	Mixeff.d	P_{FWE}
SAD wo MED vs HC	Adu	30	479	1984	ns	ns	ns	ns
SAD wo MED vs HC	Ado	27	356	771	ns	ns	ns	ns
SAD E-ONS vs HC	–	23	240	1729	ns	ns	**−0.194**	**0.009**
SAD E-ONS vs HC	Adu	15	136	1071	ns	ns	**−0.326**	**0.001**
SAD E-ONS vs HC	Ado[d]	12	98	621	–	–	–	–
SAD L-ONS vs HC	–	16	200	1174	ns	ns	ns	ns
SAD L-ONS vs HC	Adu	16	174	1078	ns	ns	ns	ns
SAD L-ONS vs HC	Ado[d]	7	22	38	–	–	–	–

Sens. sensitivity analysis by age group, *SAD* social anxiety disorder, *HC* healthy control, *L* left; *R* right, *N* number of participants, *Mixeff.d* mixed-effects d, *FWE* family-wise error correction (Bonferroni), *ns* non-significant (uncorrected $p < 0.05$), *Adu* adults, *Ado* adolescents, *ANX* any comorbid anxiety disorder, *wo* without, *MED* psychotropic medication use at time of scan, *E-ONS* early onset, *L-ONS* later onset.
[a]Results presented for all regions with an FWE significant finding in one of the full age range mega-analyses.
[b]Bold text highlights significant result after FWE multiple comparison correction.
[c]Plain text indicates uncorrected significant result.
[d]Sensitivity analyses not performed – insufficient data available.

differences in patients with SAD relative to controls, involving regions previously implicated in social approach-avoidance conflicts and the perception of threat. The most pertinent finding across the conducted mega-analyses concerned smaller volumes of the bilateral putamen in SAD patients compared to HC participants. Volumetric alterations differed across age groups: smaller volumes of the bilateral putamen and larger volumes of the bilateral pallidum were observed in adult SAD patients, but no differences were observed in adolescent SAD patients. Comorbid anxiety disorders and early age of onset were additional determinants of SAD-related volumetric alterations, revealing smaller volumes of the left amygdala and right hippocampus, respectively. Thus, heterogeneity in age and clinical characteristics may partly explain the inconsistent findings previously reported in the literature.

The smaller bilateral putamen in SAD patients aligns with the previous meta-analytic result of a smaller left putamen [24]; also see [41, 42]. In our mega-analyses, smaller putamen volumes were accompanied by larger pallidum volumes in adult SAD as well as in SAD subgroups without comorbidity or medication use, and with later onset of the condition. The sample included in a previous voxel-based morphometry mega-analysis ([23]; this sample partly overlaps with presently investigated sample) had relatively similar characteristics and showed a larger volume in the right dorsal putamen, extending into the pallidum. Enlargement of the left pallidum was also found to be positively related to social anxiety symptoms in families genetically enriched for SAD [43]. The prior mega-analytic finding [23] may therefore reflect a signal originating in the pallidum or a regional volumetric extension of the putamen adjacent to the pallidum. Future vertex-wise analysis of the shape of subcortical regions (cf. [44, 45]) might be able to locate group differences more precisely and shed light on this matter. The role of the basal ganglia complex in reward processing deficiencies has previously been emphasized in relation to inhibited temperament and anxiety in adolescence [11]. In these groups, aberrant putamen activation has been proposed to reflect an intense desire to avoid failure in social contexts. Less is known about the pallidum in relation to motivational deficiencies in SAD [11]. Thus, the functional role of the putamen and pallidum in positive and negative emotional processing in adult and adolescent SAD deserves further investigation [11, 46, 47].

The use of standardized ENIGMA protocols allows us to compare the volumetric differences observed for SAD to other psychiatric conditions previously examined with a similar approach. The combination of smaller putamen and larger pallidum volumes has not been observed for other psychiatric conditions examined in ENIGMA Working Groups [48]. The findings for SAD contrast with the subthreshold enlargement of left and right putamen volume in GAD patients previously reported by our Working Group [45]. Larger pallidum volumes, but no difference in putamen volumes, have been reported in adult OCD patients by the ENIGMA-OCD Working Group [49]. Furthermore, smaller putamen and pallidum volumes have been reported by the ENIGMA-Autism Spectrum Disorder Working Group [50]. In the present study, the effect sizes observed for SAD were small (mixed-effects *d* ranging from approximately −0.10 in the main analysis to −0.30 in late-onset SAD vs HCs; [51]). Mixed-effects *d* estimates are comparable to Cohen's *d* estimates, although mixed-effects estimates can be slightly attenuated through better adjustment for between-sample variance [35]. Effect sizes for SAD are thus comparable in magnitude to those observed in ENIGMA studies of the anxiety-related conditions OCD, PTSD, and MDD (Cohen's *d* approximately −0.15 for bilateral hippocampus in main analyses; [48, 52, 53]), but are substantially smaller than previously observed for schizophrenia (Cohen's *d* −0.46 for bilateral hippocampus [54]).

The observed smaller left amygdala in SAD patients with comorbid anxiety disorders and comorbid MDD in the present study concurs with previous findings in adolescents [17], young adults with SAD [16], and male adult SAD patients [14], although prior findings more consistently involved the right amygdala. Amygdala involvement in fear processing is possibly functionally lateralized; the right amygdala has been implicated in rapid fear responsivity whereas the left amygdala is thought to be involved in elaborate and stimulus-specific appraisals of anxiety [55–57]. The latter of these functional specializations might bear relevance to the present findings. Interestingly, concordance in genetic variation has been identified between risk for anxiety disorders and smaller amygdala volumes [58], providing a possible explanation for the more pronounced amygdala alterations in SAD patients with comorbid anxiety. Of note, the ENIGMA-MDD Working Group reported no significant differences in bilateral amygdala volumes related to MDD diagnosis or comorbid anxiety disorders. Yet, smaller volumes of the bilateral hippocampus were found in early onset MDD relative to HCs ([53]; more pronounced than in the full MDD sample), similar to the presently observed smaller right hippocampal volume in early onset SAD. The effect size for early onset SAD was substantially higher in the adult subsample compared to the full age range sample (i.e., when also including children and adolescents). This could possibly reflect an association with longer illness duration, in line with the smaller hippocampal volumes that have been observed in recurrent MDD [53].

Here, we present the largest study to date investigating subcortical volumes in SAD patients. We extend prior literature by adopting a mega-analytic approach with standardized protocols for processing and quality control across the contributing samples that facilitated comparisons with psychiatric conditions previously studied within the ENIGMA Consortium, and by utilizing our large dataset to extensively explore clinical characteristics that are associated with volumetric differences in SAD patients. While harmonization was accomplished to a certain degree, several sources of methodological heterogeneity remained (e.g., field strength, scan sequence, FreeSurfer version). Furthermore, analyses needed to be restricted to variables that were consistently collected across the samples. This resulted in a relatively modest sample size and limited variability for analyses of symptom severity, although the sample size is substantially larger than in previous studies on SAD (for example $n = 148$; [23]). Finally, limitations of the source datasets (involving cross-sectional and in part retrospective designs) also applied to the aggregated dataset. Relatively few of the SAD participants were taking psychotropic medication at the time of scan, and few no longer met diagnostic criteria for current SAD. This resulted in limited power to investigate these factors and could be suggestive of selection bias. Longitudinal research will need to delineate the trajectory of volumetric alterations in subcortical regions in SAD patients (cf. [59]), to confirm whether volumetric differences in subcortical regions are stable over time in specific clinical SAD subgroups or newly emerge following critical stages of development and possibly aggravate with longer illness duration.

To conclude, the largest coordinated multi-site analysis on subcortical volumes in SAD to date revealed subtle volumetric alterations in subcortical brain regions implicated in emotional processing in SAD, with the most noteworthy and consistent finding concerning smaller volumes in the bilateral putamen. The magnitude of these volumetric differences appears to be comparable to those observed in other anxiety-related psychiatric conditions, although the implicated subcortical regions are partly distinct. Age and clinical characteristics are probable determinants of volumetric alterations in subcortical regions in SAD patients, suggesting that these perhaps aggravate with prolonged illness duration. The ENIGMA-Anxiety Working Group will next conduct a large multi-site analysis on cortical thickness and cortical surface area in SAD, to examine whether age and clinical characteristics are determinants of alterations in these brain features as well. Further research is needed to delineate how SAD-related alterations in brain structure are associated with SAD illness

progression, investigating persistence and remission of symptoms in adolescence and adulthood.

DATA AVAILABILITY

The ENIGMA-Anxiety Working Group is open to sharing the data and code from this investigation to researchers for secondary data analysis. To request access to volumetric, clinical, and demographic data, an analysis plan can be submitted to the ENIGMA-Anxiety Working Group (http://enigma.ini.usc.edu/ongoing/enigma-anxiety/). Data access is contingent on approval by PIs from contributing samples.

CODE AVAILABILITY

Code can be requested from the corresponding author.

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