Research Paper

# Hippocampal and amygdala subfield volumes in obsessive–compulsive disorder by medication status

**Ziphozihle Ntwatwa, MSc; Christine Lochner, PhD; Annerine Roos, PhD; Tatum Sevenoaks, MSc; Jack van Honk, PhD; Marcelo C. Batistuzzo, PhD; Sunah Choi, PhD; Marcelo Q. Hoexter, MD, PhD; Minah Kim, MD, PhD; Jun Soo Kwon, MD, PhD; David Mataix-Cols, PhD; José M. Menchón, MD, PhD; Euripedes C. Miguel, MD, PhD; Takashi Nakamae, MD, PhD; Carles Soriano-Mas, PhD; Dick J. Veltman, MD, PhD; Nynke A. Groenewold, PhD; Odile A. van den Heuvel, MD, PhD; Dan J. Stein, MD, PhD; Jonathan Ipser, PhD**

**Background:** Although it has been suggested that the hippocampus and amygdala (HA) are involved in the neurobiology of obsessive–compulsive disorder (OCD), volumetric findings have been inconsistent, and little work has been undertaken on the volumetry of the heterogeneous anatomic units of HA, with their specific functions and cytoarchitecture, in OCD. We sought to explore potential sources of heterogeneity in brain volumes by performing a separate analysis for people with and without psychotropic medication use, as well as the association of subfield volumes with OCD symptom severity. **Methods:** We segmented $T_1$-weighted images from people with OCD and healthy controls in the OCD Brain Imaging Consortium to produce 12 hippocampal subfields and 9 amygdala subfields using FreeSurfer 6.0. We assessed between-group differences in subfield volume using a mixed-effects model adjusted for age and quadratic effects of age, sex, site, and whole HA volume. We also performed subgroup analyses to examine subfield volume in relation to comorbid anxiety and depression, medication status, and symptom severity. We corrected all analyses for multiple comparisons using the false discovery rate (FDR). **Results:** We included images from 381 people with OCD and 338 healthy controls. These groups did not significantly differ in HA subfield volumes. However, medicated people with OCD had significantly smaller volumes in the hippocampal dentate gyrus ($p_{FDR}$ = 0.04, $d$ = –0.26) and molecular layer ($p_{FDR}$ = 0.04, $d$ = –0.29), and larger volumes in the lateral ($p_{FDR}$ = 0.049, $d$ = 0.23) and basal ($p_{FDR}$ = 0.049, $d$ = 0.25) amygdala subfields, than healthy controls. Unmedicated people with OCD had significantly smaller volumes in the hippocampal cornu ammonis sector 1 ($p_{FDR}$ = 0.02, $d$ = –0.28) than controls. We did not detect associations between any subfield volume and OCD severity. **Limitations:** We used cross-sectional data, which limits the interpretation of our analysis. **Conclusion:** Differences in HA subfields between people with OCD and healthy controls are dependent on medication status, in line with previous work on other brain volumetric alterations in OCD. This emphasizes the importance of considering psychotropic medication in neuroimaging studies of OCD.

## Introduction

Obsessive–compulsive disorder (OCD) is a common psychiatric disorder characterized by persistent intrusive thoughts (obsessions), repetitive ritualistic overt or covert behaviours (compulsions), or both.[1] Typical obsessive thoughts concerning contamination, harm, sexual or religious ideas, and exactness are accompanied by anxiety or distress, which may, in turn, incite compulsions such as excessive cleaning, checking, ordering and arranging, and counting.[2] In the adult population, OCD has a lifetime prevalence of 1.9%–2.5%, with strong negative effects on occupational and social functioning.[3] In many cases, OCD is comorbid with other disorders, including major depressive disorder (MDD) and anxiety disorders.[3,4] Additionally, differences in symptom severity likely contribute to OCD heterogeneity.[5–7]

Neuroimaging studies suggest that OCD is associated with structural or functional changes in the cortico–striato–thalamo–cortical loops.[8,9] However, emerging evidence

**Correspondence to:** Z. Ntwatwa, Department of Psychiatry & Mental Health, Neuroscience Institute, University of Cape Town, 7925, Cape Town, South Africa; ziphozihle.ntwatwa@uct.ac.za

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suggests that OCD involves additional brain circuits, including the cerebellar, frontoparietal, and frontolimbic circuits.[9] Meta-analysis of whole-brain resting-state functional magnetic resonance imaging (fMRI) indicates hypoconnectivity within certain regions in OCD, specifically in the frontoparietal and salience networks, and between the salience, frontoparietal, and default mode networks.[10] There has also been interest in investigating the hippocampal formation and amygdala in OCD, given the established roles of these brain structures in anxiety[11–13] and fear conditioning.[14] Indeed, an fMRI study suggested that, during fear conditioning, the hippocampus has reduced activation among people with OCD,[15] and a meta-analysis indicated increased amygdala activation during emotional processing among people with OCD, compared with healthy controls (HCs).[16]

However, structural MRI studies in OCD have yielded inconsistent findings, reporting both increases and decreases in HA volumes.[17–19] Such inconsistency could be attributable to small sample sizes, the presence of comorbidities, or medication use. Medication status is an important factor, as psychotropic medications may influence brain volumes, highlighting the need to consider medication use when interpreting volumetric findings in OCD. Additionally, previous studies have investigated total HA volumes rather than subfield volumes, which may mask subtle OCD-related differences in volume that vary between the individual subfields. Work from the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) OCD Consortium (ENIGMA-OCD) found smaller hippocampal volumes among people with OCD than among HCs, but only among those on medication or with adult-onset OCD.[20] These findings were corroborated by work from the multisite OCD Brain Imaging Consortium (OBIC), which demonstrated that smaller hippocampi were associated with medication use.[21,22] In a post hoc analysis, Ivanov and colleagues[23] found smaller hippocampi and thalami and larger pallida among medicated than among unmedicated people with OCD across different age groups.

The HA comprises anatomically complex structures, consisting of multiple interconnected nuclei that can be segmented according to their cytoarchitecture, histochemistry, and connectivity profile.[24] Little, however, is known about HA subfield volumes in OCD. Recent developments in structural MRI segmentation techniques have allowed for the robust delineation of HA subfields using a Bayesian algorithm that is based on the transformation of manual segmentation to an automated atlas.[25] Indeed, a previous study showed that pediatric individuals with OCD have larger hippocampal subfields — namely in the left subiculum body, left cornu ammonis (CA) 4, left granule cell layer of the dentate gyrus (DG), left molecular layer (ML), and right parasubiculum — than HCs.[26] Recent reports indicate that medication-free people with OCD have smaller volumes in the hippocampal subiculum, presubiculum, CA 2/3, and tail,[27] and smaller volumes in the basolateral and central amygdala subfields.[28] However, these studies involved small samples and did not include people using psychotropic medication.

We set out to address inconsistencies in previous reports of volume differences in OCD by analyzing data from a large and diverse sample. We specifically aimed to explore potential sources of heterogeneity in brain volumes by performing a separate analysis for people with and without psychotropic medication use, and we studied the effect of comorbid anxiety and depression as well as the association of subfield volumes with OCD symptom severity.

## Methods

### *Participants and magnetic resonance imaging*

We obtained sociodemographic and neuroimaging data from 6 research sites as part of OBIC. Collaborating sites and participant details have been described in a previous publication.[29] Briefly, people with OCD were recruited through local outpatient clinics, whereas HCs were sourced through local advertisements. All participants were screened for *Diagnostic and Statistical Manual of Mental Disorders Fourth Edition* Axis I disorders. For the patient group, the primary diagnosis had to be OCD, but comorbidity with mood and anxiety disorders was allowed. To be included, HCs were required to be without current Axis I psychiatric disorders. Participants were excluded if they were younger than 18 years or older than 65 years; had a current psychotic disorder; or had a history of substance use disorder, intellectual disability, or severe organic or neurologic pathology. Additional data were collected on age of OCD onset, medication status, and symptom severity, assessed with the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS).[2]

### *Image analysis and segmentation*

All participants underwent 1.5 T structural $T_1$-weighted MRI.[29] Image analysis was performed on the high-performance computing cluster at the University of Cape Town, South Africa. First, we applied the standard FreeSurfer version 5.3 analysis pipeline using the recon-all function to initiate all cortical reconstruction processes (http://surfer.nmr.mgh.harvard.edu/). This function initiates bias-field correction to the $T_1$-weighted images as well as registration to Talairach space, intensity normalization, and skull stripping.[30]

Next, we performed subfield segmentation using the segmentHA_T1.sh script in FreeSurfer version 6.0. This script simultaneously segments the HA, thereby preventing structural overlap.[31] The probability atlas applied by the script is based on the transformation of ex vivo manual segmentation to an automated algorithm that segments in vivo MRI data in target space. The atlas was built using Bayesian inference based on a tetrahedral mesh spanning the amygdala and neighbouring structures.[25] For each participant, the model produces left and right volumes for the HA subfields, as well as whole HA volume and intracranial volume.

The hippocampus was segmented into the following subfields: parasubiculum, presubiculum, subiculum, CA sectors (CA1, CA2–3, CA4), DG, ML, hippocampus–amygdala transition area, fimbria, hippocampal tail, and hippocampal fissure.[31] The hippocampal subfields were grouped according to the FreeSurfer 6.0 hippocampal module without head–body subdivision, and the ML was not absorbed to the nearest DG layer (https://surfer.nmr.mgh.harvard.edu/fswiki/HippocampalSubfieldsAndNucleiOfAmygdala). We segmented the amygdala into 7 nuclei (lateral, basal, accessory basal, central, medial, cortical, paralaminar nucleus) and 2 transition areas (anterior amygdaloid area and cortico–amygdaloid transition). Studies suggest that the amygdala can be grouped in the basolateral (lateral, basal, accessory basal, paralaminar nucleus), centromedial (central and medial), and superficial area (cortical, anterior amygdaloid area, and cortico–amygdaloid transition) regions.[32] Figure 1 provides an illustration of a typical Freesurfer segmentation of the HA.

### *Quality control by visual inspection*

We used a combination of visual inspection and quantitative measures to identify inaccurate subfield segmentation. To visually identify segmentation failures, we used an adaptation of the ENIGMA Consortium Quality Control protocol for subcortical and hippocampal subfields (https://enigma.ini.usc.edu/protocols/imaging-protocols/). In brief, 3 independent raters (Z.N., A.R., T.S.) examined each scan, slice by slice, within an HTML-based image gallery for partial or atypical segmentation. A list of questionable cases was generated for 3-dimensional inspection, using the Freeview utility included with FreeSurfer.[35] We identified additional cases 2 ways. First, we *z*-standardized each subfield and excluded participants whose score exceeded plus or minus 5 standard deviations (SDs) from the mean for any subfield.[36] Next, we generated automated outliers using an R script provided by the ENIGMA-MDD working group (https://enigma.ini.usc.edu/ongoing/enigma-hippocampal-subfields). For the latter,

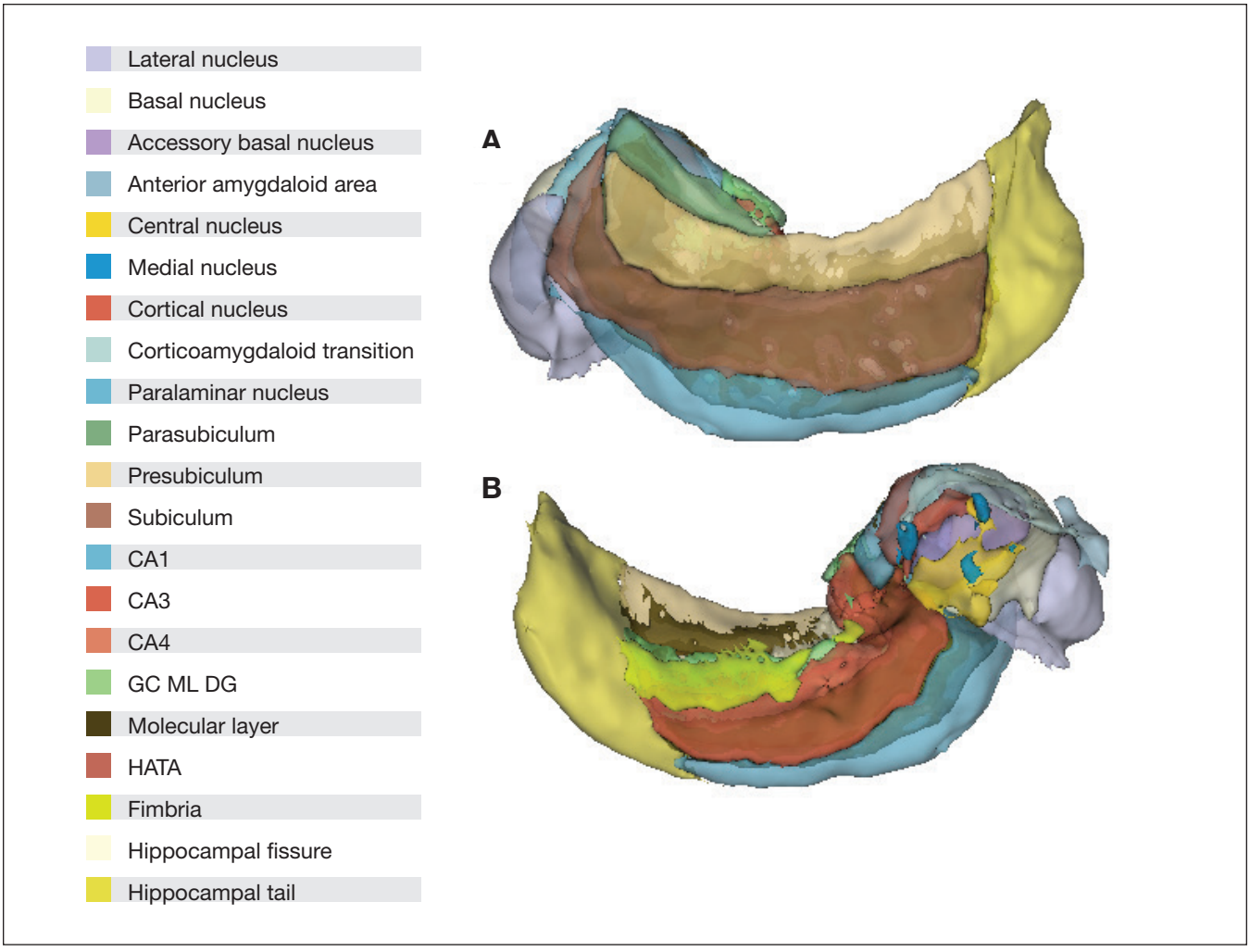


**Figure 1:** (A) Lateral and (B) medial visualization of amygdala–hippocampal Freesurfer subfield segmentation from right hemisphere of a single representative healthy control, using 3DSlicer (https://www.slicer.org/). The hippocampal fimbria was not included in our analysis.[33,34] CA = cornu ammonis; GC ML DG = granule cells in the molecular layer of the dentate gyrus; HATA = hippocampus–amygdala transition area.

participants flagged as outliers for 5 or more subfields were added to the list for 3-dimensional inspection.

### *Statistical analysis*

In addition to adjusting for age, sex, and scanner site across all analyses,[37–40] we included quadratic effects of age in the linear mixed-effects model to account for the nonlinear relationship between age and brain volumes.[41,42] In addition, we used site as a random effects variable to minimize site-related variability in MRI acquisition and patient evaluations. Although recent harmonization protocols such as ComBat[43] are increasingly popular, the use of site as a random effects variable in a mixed-effects linear regression framework has previously been demonstrated as yielding comparable results to these protocols, while avoiding the risk of potentially removing variance from factors of interest that differ by site, a known shortcoming of ComBat. Initial exploration of the data revealed a sex by age and sex by age-squared interaction for specific subfields, warranting inclusion of these terms in the mixed-effects models.

We conducted all statistical analyses in R (https://www.r-project.org/). We used the lme4 package to perform our analysis and used mixed-effects *d* effect sizes, as calculated using the *t* values from linear mixed-effects models,[44] which included a random intercept for scan site. To reduce the statistical penalty associated with correction for multiple comparisons in the main analysis, we averaged the left and right volumes to produce a single value per participant.[20] In this analysis, a total of 21 separate subfield tests were performed. In an exploratory analysis, we examined the left and right subfields separately, conducting 42 separate tests. The hemisphere-specific findings are reported in Appendix 1, available at www.jpn.ca/lookup/doi/10.1503/jpn.230119/tab-related-content. We corrected all models for the total subfield volume using the combined HA volume (as recommended in the FreeSurfer manual; https://surfer.nmr.mgh.harvard.edu/fswiki/HippocampalSubfieldsAndNucleiOfAmygdala). We corrected all analyses for multiple comparisons using the false discovery rate (FDR). To explore the potential effects of sex and age on subfield volume differences between participants with OCD and HCs, we analyzed the interaction between diagnosis and sex, as well as diagnosis and age (Appendix 1, Note 1). We performed separate analyses where we compared subgroups of interest to HCs, including participants with OCD with anxiety comorbidity, those without anxiety comorbidity, those with MDD, and those without MDD. We also included those with a history of psychotropic medication use and those without medication use. In light of preliminary evidence for subfield differences between medicated participants and HCs, we tested the robustness of these findings to the inclusion of education in the model, as a potential confound.

### *Ethics approval*

Ethics approval was obtained for each site from all local ethics review boards. Written informed consent was provided by each participant. In addition, for multisite pooling of data, approval was obtained from the medical ethical committee of the Amsterdam University Medical Center.

## Results

### *Sample characteristics*

We excluded 55 participants from the main analysis, of which we identified 40 from visual quality control, 9 based on visual quality control after outlier flags, and 6 whose *z* scores exceeded plus or minus 5 SD from the mean of any subfield (Table 1). The final sample consisted of 381 participants with OCD and 338 HCs (Table 2). In the full sample, participants with OCD were significantly older (32.0 [SD 9.4] yr v. 30.2 [SD 9.3] yr; $t = -2.5$, $p = 0.01$) and had less education (13.7 [SD 2.8] yr v. 14.6 [SD 3.4] yr; $t = 3.6$, $p < 0.001$) than HCs. Moreover, both age and education level were significantly associated with volume across the entire sample for a number of HA subfields (Appendix 1, Table S4). There were

**Table 1: Number of scans provided and excluded for participants with obsessive–compulsive disorder and healthy controls after quality checking**

| | Initial no. of scans* | | | Excluded for missing data | | | Excluded after visual QC | | | Reasons for exclusion | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Site | OCD | HC | Total | OCD | HC | Total | OCD | HC | Total | Segmentation† | QC + outlier‡ | *z* score§ |
| Amsterdam | 53 | 49 | 102 | 1 | 1 | 2 | 4 | 1 | 5 | 4 | 1 | 0 |
| Barcelona | 86 | 102 | 188 | 0 | 0 | 0 | 9 | 6 | 15 | 9 | 4 | 2 |
| Brazil | 58 | 40 | 98 | 1 | 1 | 2 | 6 | 2 | 8 | 13 | 2 | 1 |
| Japan | 88 | 48 | 136 | 2 | 5 | 7 | 5 | 3 | 8 | 12 | 0 | 2 |
| Korea | 87 | 97 | 184 | 0 | 0 | 0 | 5 | 9 | 14 | 0 | 0 | 0 |
| London | 44 | 33 | 77 | 0 | 0 | 0 | 2 | 3 | 5 | 2 | 2 | 1 |
| Total | 416 | 369 | 785 | 4 | 7 | 11 | 31 | 24 | 55 | 40 | 9 | 6 |

HC = healthy control; OCD = obsessive–compulsive disorder; QC = quality control.
*Reported in previous publication.[29]
†Participants excluded based on visual screening for partial or atypical segmentation using an adaptation of the Enhancing Neuroimaging Genetics through Meta-Analysis Consortium Quality Control protocol for subcortical and hippocampal subfield (https://enigma.ini.usc.edu/ongoing/enigma-hippocampal-subfields/).
‡Participants excluded based on R script flag for abnormalities on more than 5 subfields and flagged for visual QC.
§Participants excluded based on exceeding plus or minus 5 standard deviations from the *z*-standardized mean of any of the subfields.

no significant group differences in sex and whole HA volume. The mean Y-BOCS score in the OCD group was 24.9 (SD 6.2).

We performed separate analyses of subgroups of interest to HCs, including participants with OCD with comorbid anxiety ($n$ = 74), those without comorbid anxiety ($n$ = 356), those with MDD ($n$ = 95), and those without MDD ($n$ = 286). We also included those with a history of psychotropic medication use ($n$ = 161), and those without medication use ($n$ = 220). Table 3 provides details on demographic and clinical characteristics of subgroups.

### *Group difference in subfield volumes*

We conducted between-group comparisons of all participants with OCD and HCs. There were no significant differences in HA subfield volumes ($p_{FDR} < 0.05$) after adjusting for age and quadratic effects of age, sex, site, and whole HA volume (Figure 2A and Table 4). In the exploratory analysis, there were no significant differences in left or right HA subfield volumes ($p_{FDR} < 0.05$) after adjusting for age and quadratic effects of age, sex, site, and whole left and right HA volume (Appendix 1, Table S1B).

### *Association of subfields volume and clinical factors*

Medicated participants with OCD ($n$ = 161) had significantly smaller hippocampal DG volumes ($p_{FDR}$ = 0.04, $d$ = –0.26) and ML ($p_{FDR}$ = 0.04, $d$ = –0.29), and larger lateral ($p_{FDR}$ = 0.049, $d$ = 0.23) and basal ($p_{FDR}$ = 0.049, $d$ = 0.25) amygdala volumes, compared with HCs ($n$ = 291) (Figure 2B). Unmedicated participants with OCD ($n$ = 220) had significantly smaller hippocampal CA1 subfield volumes ($p_{FDR}$ = 0.02, $d$ = –0.28) than HCs ($n$ = 220). There were no significant subfield volume differences between medicated and unmedicated participants with OCD (Appendix 1, Note 1 and Table S3).

In an additional sensitivity analysis that included education as a covariate, none of the significant differences in subfield volumes between medicated participants with OCD and HCs (DG, ML, lateral amygdala, and basal amygdala), or between unmedicated participants and HCs (CA1) remained significant after adjusting for multiple comparisons. Nevertheless, all of these findings were significant when using unadjusted $p$ values ($p < 0.05$) and demonstrated relatively large effect sizes ($d > \pm 0.2$). Moreover, in models comparing medicated participants with OCD versus HCs that included education with those that did not, we observed comparable effect size

**Table 2: Demographic and clinical characteristics of participants with obsessive–compulsive disorder and healthy controls**

| Characteristic | No. (%) of participants* | | $t$ | df | $p$ value |
|---|---|---|---|---|---|
| | Participants with OCD $n$ = 381 | HC $n$ = 338 | | | |
| Age, yr, mean ± SD | 32.0 ± 9.4 | 30.2 ± 9.3 | –2.5 | 708.7 | 0.01 |
| Education, yr, , mean ± SD | 13.7 ± 2.8 | 14.6 ± 3.4 | 3.6 | 653 | < 0.001 |
| Y-BOCS total score, mean ± SD | 25 ± 6.2 | – | | | |
| Age at onset of OCD, yr, mean ± SD† | 20.3 ± 8.8 | – | | | |
| Total hippocampal volume, mean ± SD | 3544.4 ± 340.4 | 3587.5 ± 361.6 | 1.6 | 694.4 | 0.1 |
| Total amygdala volume, mean ± SD | 1770.3 ± 187.9 | 1783 ± 198.1 | 0.8 | 696.3 | 0.4 |
| Sex, male | 186 (48.8) | 179 (52.9) | –1.1 | 707 | 0.3 |
| Right-handed | 327 (85.8) | 303 (89.6) | | | |
| Medication use at time of scan | 161 (43.6) | – | | | |

df = degrees of freedom; HC = healthy control; OCD = obsessive–compulsive disorder; SD = standard deviation; Y-BOCS = Yale–Brown Obsessive Compulsive Scale.
*Unless indicated otherwise.
†As measured by the Y-BOCS symptom checklist.

**Table 3: Demographic and clinical characteristics of subgroups**

| Characteristic | No. (%) of participants | | | | | | | Comparison |
|---|---|---|---|---|---|---|---|---|
| | A: With OCD on medication $n$ = 161 | B: With OCD not on medication $n$ = 220 | C: With OCD with anxiety $n$ = 74 | D: With OCD without anxiety $n$ = 356 | E: With OCD with MDD $n$ = 95 | F: With OCD without MDD $n$ = 286 | G: HC $n$ = 338 | |
| Age, yr, mean ± SD | 32.89 ± 9.13 | 31.33 ± 9.54 | 32.27 ± 8.67 | 31.81 ± 9.39 | 34.99 ± 9.56 | 30.99 ± 9.14 | 30.2 ± 9.3 | A > G<br>C > G<br>D > G |
| Education, yr, mean ± SD | 12.90 ± 2.88 | 14.33 ± 2.62 | 13.40 ± 2.97 | 13.63 ± 2.81 | 13.48 ± 2.92 | 13.78 ± 2.79 | 14.6 ± 3.4 | A > G<br>D > G<br>E > G<br>F > G |
| Sex, male | 83 (51.55) | 103 (46.81) | 32 (43.24) | 179 (50.28) | 32 (33.68) | 154 (53.84) | 179 (52.9) | C > G<br>E > G |

HC = healthy control; MDD = major depressive disorder; OCD = obsessive–compulsive disorder; SD = standard deviation.

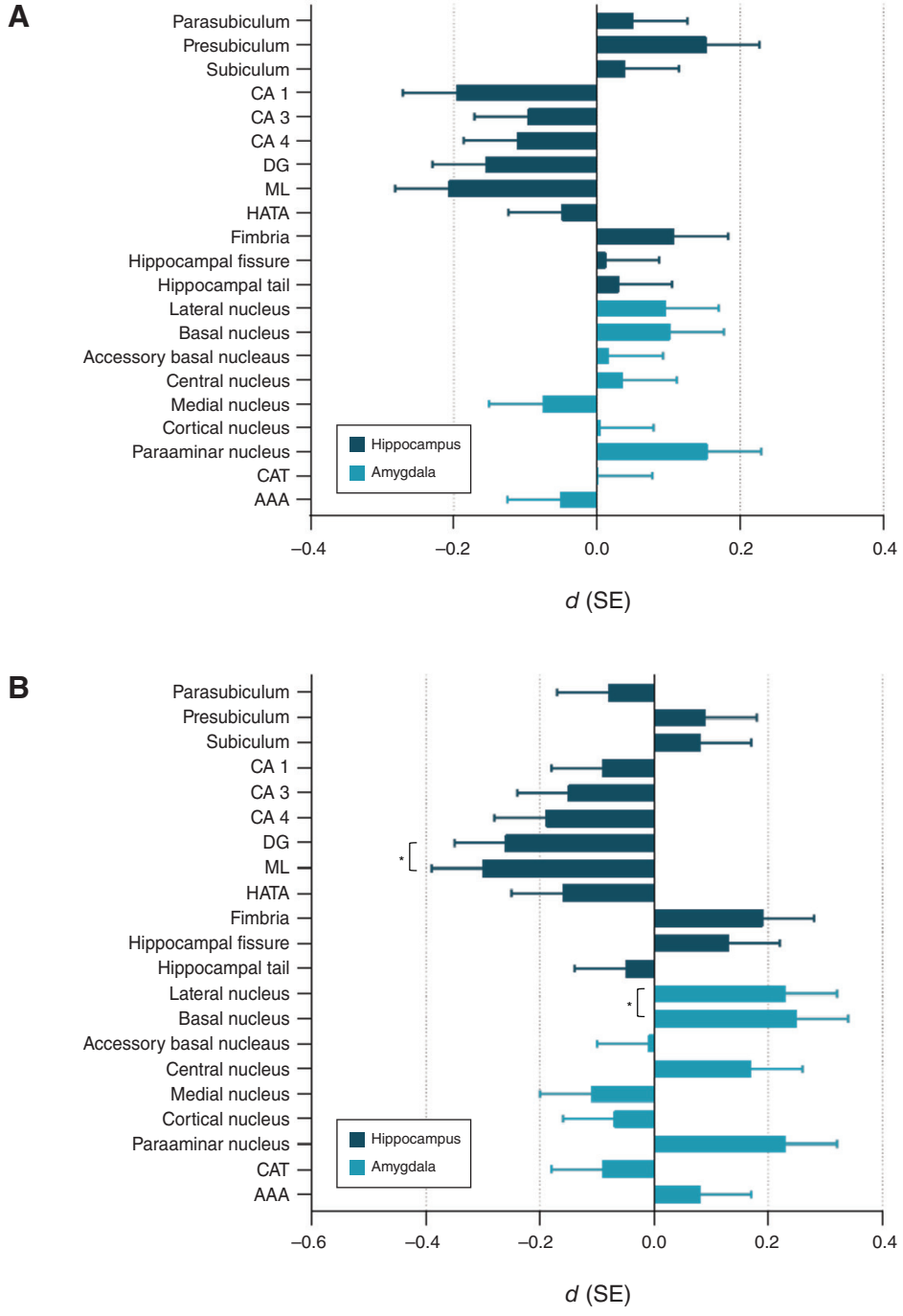


**Figure 2:** (A) Mixed effect size estimates (*d*) for hippocampal and amygdala subfield volumes between participants with obsessive–compulsive disorder (OCD; *n* = 381) and healthy controls (*n* = 338) and (B) between medicated participants with OCD (*n* = 161) and healthy controls (*n* = 291). Data presented with standard errors (SEs). *$p < 0.05$. AAA = anterior amygdaloid area; CA = cornu ammonis; CAT = corticoamygdaloid transition area; DG = granule cell layer of dentate gyrus; HATA = hippocampus–amygdala transition area; ML = molecular layer. Supporting data are presented in Table 4 and Appendix 1, Tables S1.1a and S1.7a.

**Table 4: Mixed effect size estimates for hippocampal and amygdala subfield volumes between individuals with obsessive–compulsive disorder (*n* = 381) and healthy controls (*n* = 338)**

| Subfield | Mixed effects *d* | SE | *p* value (uncorrected) | *p* value (corrected)* |
|---|---|---|---|---|
| Hippocampal subfields | | | | |
| Parasubiculum | 0.051 | 0.075 | 0.443 | 0.664 |
| Presubiculum | 0.152 | 0.075 | 0.037 | 0.156 |
| Subiculum | 0.039 | 0.075 | 0.540 | 0.756 |
| CA1 | –0.196 | 0.075 | 0.006 | 0.063 |
| CA3 | –0.096 | 0.075 | 0.164 | 0.353 |
| CA4 | –0.111 | 0.075 | 0.104 | 0.353 |
| DG | –0.155 | 0.075 | 0.023 | 0.150 |
| ML | –0.207 | 0.075 | 0.003 | 0.060 |
| HATA | –0.049 | 0.075 | 0.363 | 0.636 |
| Fimbria | 0.108 | 0.075 | 0.122 | 0.353 |
| Hippocampal fissure | 0.012 | 0.075 | 0.864 | 0.955 |
| Hippocampal tail | 0.030 | 0.075 | 0.681 | 0.841 |
| Amygdala subfields | | | | |
| Lateral nucleus | 0.095 | 0.075 | 0.168 | 0.353 |
| Basal nucleus | 0.102 | 0.075 | 0.149 | 0.353 |
| Accessory basal nucleus | 0.017 | 0.075 | 0.802 | 0.935 |
| Central nucleus | 0.036 | 0.075 | 0.631 | 0.828 |
| Medial nucleus | –0.076 | 0.075 | 0.296 | 0.564 |
| Cortical nucleus | 0.004 | 0.075 | 0.956 | 0.979 |
| Paralaminar nucleus | 0.154 | 0.075 | 0.029 | 0.150 |
| CAT | 0.002 | 0.075 | 0.979 | 0.979 |
| AAA | –0.050 | 0.075 | 0.419 | 0.664 |

AAA = anterior amygdaloid area; CA = cornu ammonis; CAT = corticoamygdaloid transition area; DG = granule cell layer of dentate gyrus; HATA = hippocampus–amygdala transition area; ML = molecular layer; OCD = obsessive–compulsive disorder; SE = standard error.
*Corrected for for multiple comparisons using the false discovery rate.

estimates (lateral amygdala: –0.21 v. 0.23; basal amygdala: –0.23 v. 0.25; DG: –0.26 v. –0.26; ML: –0.27 v. –0.30). The same pattern was observed with respect to the model comparing unmedicated participants with HCs (CA1: –0.25 v. –0.28). Perhaps most importantly, education was not a statistically significant predictor of subfield volume (all unadjusted $p > 0.05$) in the mixed-effects model for any of the 5 models for which group effects were observed, indicating that much of the variability in subfield volume explained by education in the bivariate analyses (Appendix 1, Table S4) was shared with other covariates included in the models.

There were no significant differences in HA subfield volumes between HCs ($n = 338$) and participants with OCD with ($n = 95$) or without ($n = 286$) MDD, nor those with OCD with ($n = 74$) or without anxiety comorbidity ($n = 356$).

We also tested whether subfield volumes were influenced by OCD symptom severity. We found no significant association between the volume of subfields and Y-BOCS scores (Appendix 1, Table S2).

## Discussion

We report findings from a large neuroimaging study of HA subfield volumes in OCD. We did not detect any significant differences between participants with OCD and HCs in HA subfield volumes after correction for multiple comparisons. We did observe an apparent medication effect, however, in that compared with HCs, medicated participants with OCD had both smaller volumes in the DG and ML of the hippocampal formation and larger volumes in the lateral and basal amygdala. Unmedicated participants with OCD, on the other hand, had smaller hippocampal CA1 volume than HCs. Our findings affirm previous work demonstrating medication effects on subcortical brain volumes in OCD, suggesting that medication status is a robust confounding factor that may influence the ability to detect neuroanatomical abnormalities in OCD.[20,45,46]

Our finding that volumes in the hippocampal DG and ML subfields were significantly smaller among medicated participants with OCD than among HCs is consistent with previous ENIGMA-OCD studies showing smaller hippocampi among medicated people with OCD.[20,21,23] The finding that medicated participants demonstrated smaller volumes in the hippocampal subiculum, presubiculum, and tail is not consistent with the literature. However, this discrepancy may be partially explained by previous studies that employed smaller sample sizes and did not account for clinical characteristics.[27]

Although cross-sectional structural MRI has limited capacity to identify the underlying mechanisms associated with our observations, there are a few possible explanations to be considered. In rodent studies, the DG supports hippocampal-based neurogenesis, which in turn influences hippocampal plasticity.[47–50] Adult neurogenesis — the ability of the adult

brain to form new neurons — has been shown to be modulated by various antidepressants.[51] Early work involving rodents demonstrated that antidepressants increased proliferation in hippocampal-based neurogenesis, which is suggested to be essential for the behavioural effects of antidepressants[51,52] These findings are in contrast to our observation of smaller DG and ML hippocampal volumes among people with OCD. Possible explanations for our findings include the (not mutually exclusive) possibilities that prolonged exposure to psychopharmacological agents may be neurotoxic, or that individuals with OCD who have brain abnormalities or more severe OCD may be more likely to receive treatment with medication. It should be noted, however, that in our sample, we were unable to detect an association between OCD symptom severity and volume for any of the subfields.

There is also evidence that the human amygdala may be involved in postnatal neurogenesis with cell turnover rates that are comparable to the hippocampus.[53,54] Rodent studies indicate that the lateral and basal amygdala contain immunoreactive neural cell adhesion molecules that could allow for the amygdala to participate in neuronal plasticity.[55] Additional work involving rodents and nonhuman primates demonstrates that antidepressant-modulated neurogenesis enhances neuronal and glial cell growth in the amygdala.[56,57] Although some research has shown an association between OCD and marked levels of proinflammatory cytokines[58] and neuroinflammation,[59] cell culture studies demonstrate that psychotropic medication inhibits microglial activation and subsequent release of proinflammatory cytokines, suggesting that psychotropic medication may offer neuroprotective benefits by reducing neuroinflammation.[60] Although it is tempting to interpret the larger subfield volumetric differences that we observed in medicated individuals as supporting a neuroprotective effect of treatment for OCD, it was not possible to exclude the possibility that the observed reduction in volumes reflects neuronal cell death resulting from treatment with medication. Further investigation is required to elucidate the effects of medication on subcortical volumes in OCD.

Another finding was that unmedicated participants with OCD had smaller hippocampal CA1 volumes than HCs. In contrast, other studies comparing medication-free people with OCD to HCs have typically observed smaller volumes in the hippocampal subiculum, presubiculum, and CA2/3 in OCD.[27] We speculate that smaller CA1 volumes may be a response to stress, as the CA1 is susceptible to stress-induced atrophy.[61,62] Indeed, chronic stress has been shown to reduce the volume of the CA1 in rodents.[63]

Prolonged exposure to stress hormones like cortisol may lead to a reduction in hippocampal volume by suppressing neurogenesis and enhancing neuronal atrophy.[64] Our findings are more consistent with greater atrophy, as opposed to inhibited neurogenesis, playing a mechanistic role, as rodent studies demonstrate that inhibiting neurogenesis reduces the volume of the DG and CA3, with no evidence of comparable effects for the CA1.[63] Chronic stress in rodents has been shown to increase anxiety-like behaviours and reduce the expression of metabotropic glutamate receptor 5 in the CA1. The modulation of glutamate receptors in CA1 pyramidal neurons was observed to alter stress-induced anxiety-like behaviour.[65] However, in our study, we had insufficient data to confirm that unmedicated people experienced greater stress than those taking medication.

Other rodent studies using the quinpirole sensitization model of OCD showed a downregulation of neurons expressing activity-regulated cytoskeleton-associated protein (a marker of plasticity-related neuronal activity) in the CA1 during stereotypical checking behaviour. Moreover, confocal imaging showed that the CA1 was less active during stereotypical checking in sensitized rats compared with controls. Taken together, these findings suggest that the hippocampus may be more involved in OCD than previously thought.[66]

### *Limitations*

Even with automated segmentation, the small size of the amygdala poses challenges in accurately identifying its borders.[67] We also note that there is some evidence of poor test–retest reliability in segmentation of some hippocampal structures, including the medial, paralaminar nucleus, hippocampal fissure, and fimbria.[33] These factors may limit power to detect group differences for these structures, even with the relatively large sample employed in this study. The cross-sectional nature of our study limits our interpretation of the effects of medication on subcortical volumes in OCD, as these findings require validation using longitudinal studies. Given a lack of detailed information on medication history, we were unable to further investigate the effects of medication type, dosage, and duration on subfield volumes. Additionally, although our main analysis identified significant differences between people with OCD and HCs, when the former were stratified by medication status, these findings did not remain significant when education was included as a covariate in the mixed-effects model. This is likely related to loss of power and highlights the need for future research with well-matched subgroups and comprehensive data on potential confounders. We could not account for heterogeneity in the clinical presentation of OCD in our models, particularly in light of published evidence that suggests an association between OCD symptom profile and hippocampal volume.[68] Lastly, since our study used secondary data, we had access to only 1.5 T MRI, which is lower in resolution than 3 T MRI and may have further hindered attempts to detect group differences in what are relatively small structures.

## Conclusion

The association between medication status and volumetric alterations in OCD is consistent with previous work and emphasizes the importance of considering medication use as an important confounder in neuroimaging findings. Further investigation is required to elucidate the association between medication type, dosage, and duration and brain volumes in OCD over time.

**Affiliations:** From the Department of Psychiatry & Mental Health, Neuroscience Institute, University of Cape Town, Cape Town, South Africa (Ntwatwa, Roos, Sevenoaks, van Honk, Groenewold, Stein, Ipser); the SAMRC Unit on Risk & Resilience in Mental Disorders, Department of Psychiatry, Stellenbosch University, Stellenbosch, South Africa (Lochner); the Department of Psychology, Utrecht University, Utrecht, The Netherlands (van Honk); the Department of Psychiatry and Department of Anatomy & Neuroscience, Amsterdam UMC, Vrije Universiteit, Amsterdam, The Netherlands (Veltman, van den Heuvel); the Compulsivity Impulsivity and Attention program, Amsterdam Neuroscience, Amsterdam, The Netherlands (Veltman, van den Heuvel); the Bellvitge Biomedical Research Institute-IDIBELL, Department of Psychiatry, Bellvitge University Hospital, Department of Clinical Sciences, Bellvitge Campus, Universitat de Barcelona-UB, CIBERSAM, Carlos III Health Institute, Madrid, Spain (Menchón); the Bellvitge Biomedical Research Institute-IDIBELL, Department of Psychiatry, Bellvitge University Hospital, Department of Social Psychology and Quantitative Psychology, Institute of Neurosciences, Universitat de Barcelona-UB, CIBERSAM, Carlos III Health Institute, Madrid, Spain (Soriano-Mas); the Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden (Mataix-Cols); the Stockholm Health Care Services, Region Stockholm, Stockholm, Sweden (Mataix-Cols); the Department of Clinical Sciences, Lund University, Lund, Sweden (Mataix-Cols); the Department of Psychiatry, Graduate School of Medical Science, Kyoto Prefectural University of Medicine (Nakamae); the Institute of Human Behavioral Medicine Psychiatry, Department of Psychiatry, Seoul National University College of Medicine, Seoul, South Korea (Choi, Kim, Kwon); the Department of Brain and Cognitive Sciences, Seoul National University College of Natural Sciences, Seoul, Republic of Korea (Choi); the Department of Psychiatry, Faculty of Medicine, University of São Paulo, São Paulo, Brazil (Batistuzzo, Hoexter, Miguel); the Department of Methods and Techniques in Psychology, Pontifical Catholic University, São Paulo, SP, Brazil (Batistuzzo); the SAMRC Unit on Risk & Resilience in Mental Disorders, Department of Psychiatry, University of Cape Town, Cape Town, South Africa (Stein).

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