Hippocampal and amygdala subfield volumes in obsessive-compulsive disorder differ according to medication status.

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Abstract

Intro: 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. Furthermore, the HA consist of heterogenous anatomic units with specific functions and cytoarchitecture, and little work has been undertaken on the volumetry of these subfields in OCD. Methods: T1-weighted images from 381 patients with OCD and 338 healthy controls (HCs) from the OCD Brain Imaging Consortium were segmented to produce twelve hippocampal subfields and nine amygdala subfields using FreeSurfer 6.0. We assessed between-group differences in subfield volume using a mixed-effects model adjusted for age, quadratic effects of age, sex, site, and whole HA volume. Given evidence of confounding effects of clinical characteristics on brain volumes in OCD, we also performed subgroup analyses to examine subfield volume in relation to comorbid anxiety and depression, medication status, and symptom severity. Results: Patients with OCD and HCs did not significantly differ in HA subfield volume. However, medicated patients with OCD had significantly smaller hippocampal dentate gyrus ($p_{FDR}=0.042$, $d=-0.26$) and molecular layer ($p_{FDR}=0.042$, $d=-0.29$) and larger lateral ($p_{FDR}=0.049$, $d=0.23$) and basal ($p_{FDR}=0.049$, $d=0.25$) amygdala subfields than HCs. Unmedicated patients had significantly smaller hippocampal CA1 ($p_{FDR}=0.016$, $d=-0.28$) than HCs. No association was detected between any subfield volume and OCD severity. Conclusion: Differences in HA subfields between OCD and HCs 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.

Keywords: Obsessive-Compulsive Disorder, Magnetic Resonance Imaging, hippocampal subfields, amygdala subfields, medication status.
1. Introduction

Obsessive-compulsive disorder (OCD) is a common psychiatric disorder characterized by persistent intrusive thoughts (obsessions) or repetitive ritualistic overt or covert behaviours (compulsions), or both (APA, 2022). 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, and, ordering and arranging, and counting (Goodman et al., 2014). OCD has a lifetime prevalence of 1.9% to 2.5% in the adult population with strong negative impact on occupational and social functioning (Ruscio et al., 2010). In many cases, OCD is comorbid with other disorders, including major depressive disorder (MDD) and anxiety disorders (Nazeer et al., 2020; Ruscio et al., 2010). Additionally, differences in symptom severity are likely to contribute to OCD heterogeneity (Mataix-Cols et al., 2005; Stein et al., 2019; van Oudheusden et al., 2020).

Neuroimaging studies suggest that OCD is associated with structural and/or functional changes in the cortico-striato-thalamo-cortical loops (CSTC) (Pauls et al., 2014; van den Heuvel et al., 2016). However, emerging evidence suggests that OCD involves additional brain circuits including the cerebellar, fronto-parietal, and fronto-limbic circuits (van den Heuvel et al., 2016). There has also been interest in investigating the hippocampal formation and amygdala in OCD, given the established roles of these brain structures in anxiety (Brühl et al., 2014; González-García & Visser, 2023; Shi et al., 2023) and fear conditioning (Cheng et al., 2003). Indeed, an fMRI study suggested that during fear conditioning, the hippocampus has reduced activation in patients with OCD compared to healthy controls (HCs) (Milad et al., 2013), and a meta-analysis indicated increased amygdala activation during emotional processing in patients with OCD versus HCs (Thorsen et al., 2018).

However, structural MRI studies in OCD have yielded inconsistent findings, reporting both increases and decreases in HA volumes (Kwon et al., 2004; Pujol et al., 2004; Atmaca et al., 2008; Rao et al., 2018). Such inconsistency could be attributable to small sample sizes, the presence of comorbidities, or medication use. Additionally, previous studies investigated whole HA volumes rather than investigating subfield volumes, which may not reveal subtle OCD-related differences in volume when these vary between the individual subfields. Work from the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) OCD Consortium (ENIGMA-OCD), a large brain imaging consortium, found smaller hippocampal volumes in medicated patients with OCD compared to HCs, which was also related to adult-onset OCD and comorbid depression (Boedhoe et al., 2017). These findings were corroborated by work from the multisite OCD Brain Imaging Consortium (OBIC) which demonstrated that smaller hippocampi were associated with medication use (Fouche et al., 2017; Fouche et al., 2022).

The HA are anatomically complex structures, consisting of multiple interconnected nuclei that can be segmented according to their cytoarchitecture, histochemistry and connectivity profile (Sah et al.,
2003), however little is known about hippocampal and amygdala 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 (Saygin et al., 2017). Indeed, a previous study showed that paediatric patients with OCD have larger hippocampal subfields, i.e., the left subiculum body, left cornu ammonis (CA) 4, left granule cell layer of dentate gyrus, left molecular layer, and right parasubiculum, compared to HCs (Vattimo et al., 2021). Recent reports indicate that medication-free patients with OCD have smaller volumes in the hippocampal subiculum, presubiculum, CA2/3 and tail (Zhang et al., 2019) and smaller basolateral and central amygdala subfield volumes (Zhang et al., 2020). However, these studies were conducted in smaller sample sizes, and did not include patients with psychotropic medication use.

To the best of our knowledge, this is the first study to investigate HA subfield volume in a large international multi-site sample of adult patients with OCD (n=381) and HCs (n=338). We utilized the automated segmentation algorithm on T1-weighted MRI scans to segment the HA into 12 and 9 subfields, respectively. Given the evidence of the potential confounding effects of clinical characteristics on brain volumes, we performed separate analysis for patients with and without psychotropic medication use and studied the effect of comorbid anxiety and depression. We also studied the association of subfield volumes with OCD symptom severity.
2. Methods

2.1. Participants and MRI acquisition

Sociodemographic and neuroimaging data were obtained from six research sites as part OBIC. Collaborating sites and participant details have been described in-depth in a previous publication (De Wit et al., 2014). Briefly, patients with OCD were recruited through local outpatient clinics, whereas HCs were sourced through local advertisements. All participants were screened for DSM-IV Axis I disorder. For the patient group, the primary diagnosis had to be OCD, but comorbidity with mood and anxiety disorders was allowed. To be included, healthy participants were required to be without current Axis I psychiatric disorders. Participants were excluded if they were younger than 18 or older than 65 years, had a current psychotic disorder, history of substance use disorder, intellectual disability and severe organic or neurological pathology. Additional data was collected on age of OCD onset, medication status and symptom severity (assessed with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS)) (Goodman et al., 1989) (see Table 1A). Approval was obtained per site from all local ethical review boards and written informed consent was provided by each participant. In addition, for multisite pooling of data, approval was obtained from the medical ethical committee Amsterdam, University Medical Center (UMC).

2.2. MRI image analysis and segmentation

All participants underwent 1.5-T structural T1-weighted MRI scanning (for scan parameters and scan sequences see De Wit et al., 2014). MRI image analysis was performed on the high-performance computing (HPC) cluster at the University of Cape Town, South Africa. First, we applied the standard FreeSurfer v5.3 analysis pipeline using recon-all to initiate all cortical reconstruction processes http://surfer.nmr.mgh.harvard.edu/). Recon-all initiates bias-field correction to the T1-weighted images, as well as registration to Talairach space, intensity normalisation and skull stripping (Fischl et al., 2002).

Next, subfield segmentation was performed using the segmentHA_T1.sh script in FreeSurfer v6.0. This script simultaneously segments the HA, thereby preventing structural overlap (Iglesias et al., 2015). 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 (Saygin et al., 2017). For each participant the model produces left and right volumes for the HA subfields as well as whole HA volume and intracranial volume (ICV).

The hippocampus was segmented as follows: parasubiculum, presubiculum, subiculum, cornu ammonis (CA) sectors, CA1, CA2-3, CA4, dentate gyrus (DG), molecular layer (ML), hippocampus–amygdala
transition area (HATA), fimbria, hippocampal tail, and hippocampal fissure (Iglesias et al., 2015). 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 (see https://surfer.nmr.mgh.harvard.edu/fswiki/HippocampalSubfieldsAndNucleiOfAmygdala). The amygdala was segmented into 7 nuclei (lateral (LA), basal (BA), accessory basal (AB), central (Ce), medial (Me), cortical (Co), paralaminar nucleus (PL)) and 2 transition areas (anterior amygdaloid area (AAA) and cortico-amygdaloid transition (CAT)). Schmitz-Koep et al., 2021 suggests that the amygdala can be grouped in the following three regions: basolateral ((BLA) lateral, basal, accessory basal, paralaminar nucleus), centro-medial (central and medial), and superficial area ((SFA) cortical, AAA and CAT). Shown in Figure 1 is an example of HA Freesurfer segmentation.

2.3. Quality control: 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, three independent raters (ZN, AR, TS) examined each scan, slice-by-slice, within a html-based image gallery for partial or atypical segmentation. A list of questionable cases was generated for 3D inspection, using the Freeview utility included with FreeSurfer (Sämann et al., 2022). Additional cases were identified as follows: 1) we z-standardized each subfield and excluded participants whose score exceeded ± 5 SD from the mean (van der Meer et al., 2018, supplemental data); and 2) we generated automated outliers using a R script provided by ENIGMA-MDD working group (https://enigma.ini.usc.edu/ongoing/enigma-hippocampal-subfields). For the latter, participants flagged as outliers for 5+ subfields were added to the list for 3D inspection.

As shown in Table 2, 55 participants were excluded from the main analysis, i.e., 40 participants from visual QC, an additional 9 participants based on both visual QC after outlier flags, and 6 participants as their z-scores exceeded ±5SD from the mean of any subfield. The final sample consisted of 381 patients with OCD and 338 HCs.

2.4. Statistical analysis

2.4.1. Covariate selection

In addition to adjustment for age, quadratic effects of age, sex, and scanner site across all analyses (Barnes et al., 2010; Chen et al., 2018; Nordenskjöld et al., 2013; Sargolzaei et al., 2015), we also included those covariates that demonstrated an association with HA volumes in specific models (see supplemental data).
2.4.2. Linear mixed-effects models

All statistical analyses were conducted in R (https://www.r-project.org/). We used the R package lme4 to perform our analysis and outputted mixed-effects $d$ effect sizes, as calculated using the $t$ values from linear mixed effects models (equation 22, Nakagawa & Cuthill, 2007) that included a random intercept for scan site. We averaged the left and right hemisphere volumes to produce a single value per participant (Boedhoe et al., 2017). In total, tests were performed for 21 separate subfields. All analysis were corrected for multiple comparison across 21 subfields using the false discovery rate (FDR). 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 performed separate analysis where we compared subgroups of interest to HCs, including patients with OCD without anxiety comorbidity ($n=356$), those with of MDD ($n=95$), those without MDD ($n=286$), those with a history of psychotropic medication use ($n=161$), and those without medication use ($n=220$). We did not include patients with OCD with anxiety comorbidity ($n=25$) due to low sample size.
3. Results

3.1. Sample characteristics

In the full sample (OCD: n=381; HC: n=338, see Table 1A), patients with OCD were significantly older (OCD: 32.0 years (SD = 9.4); HCs: 30.2 years (SD =9.3), t = -2.5, p = 0.012) and on average, had lower education level (OCD: 13.7 years (SD=2.8); HCs (14.6 years (SD =3.4), t = 3.6, p < 0.001) than HCs. There were no significant differences in sex and whole HA volume between patients with OCD and HCs. The mean Y-BOCS score for patients with OCD was 24.9 (SD=6.2). See Table 1B for details on demographic and clinical characteristics of subgroup patients with OCD.

3.2. Group difference in subfield volumes

Between group comparisons were conducted on 381 patients with OCD and 338 HCs. There were no significant differences in HA subfield volumes (p < 0.05, FDR-corrected), after adjusting for age, quadratic effects of age, sex, site, and whole HA volume, between patients with OCD and HCs (Figure 2A/Table 3). There were no group by age interaction effects for all subfield volumes.

3.3. Subgroup analysis: association of subfields volume and clinical factors

3.3.1. Psychotropic medication

Medicated patients with OCD (n=161) had significantly smaller hippocampal DG ($p_{FDR}= 0.042, d=-0.26$) and ML ($p_{FDR}= 0.042, d=-0.29$), and larger LA ($p_{FDR}= 0.049, d=0.23$) and BA ($p_{FDR}= 0.049, d=0.25$) amygdala, compared to HCs (n=291) (Figure 2B). Unmedicated patients with OCD (n=220) had significantly smaller hippocampal CA1 subfield volumes ($p_{FDR}= 0.016, d=-0.28$) than HCs (n=338).

3.3.2. Anxiety and MDD comorbidity

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

3.3.3. Symptom severity

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 (see supplemental data).
4. Discussion

In this paper we report findings from the largest neuroimaging study of HA subfield volumes in OCD conducted to date. While we did not detect any significant differences between patients with OCD and HCs in HA subfield volumes after multiple comparison correction, one key finding emerged from our analysis. We found that, compared to HCs, medicated patients with OCD had both smaller volumes in the DG and ML of the hippocampal formation and larger volumes in the LA and BA amygdala. 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 (Boedhoe et al., 2017; van den Heuvel et al., 2022; Weeland et al., 2022).

Our finding, that the hippocampal subfield DG and ML were significantly smaller in medicated patients with OCD than in HCs, is consistent with previous ENIGMA-OCD studies showing smaller hippocampi in medicated patients with OCD (Boedhoe et al., 2017; Fouche et al., 2017; Ivanov et al., 2022). However, our findings contradict studies showing smaller volumes in the hippocampal subiculum, presubiculum and tail in patients with OCD compared to HCs, although these studies were performed in smaller sample sizes and did not include clinical characteristics (Zhang et al., 2019). In rodent studies, the DG supports hippocampal-based neurogenesis which in turn influences hippocampal plasticity (Malberg et al., 2000; Mandyam, 2013; Perera et al., 2007; Wang et al., 2008), and there is evidence that antidepressants increase proliferation in hippocampal-based neurogenesis (McEwen, 1999; Santarelli et al., 2003). These findings are in contrast to our observation of smaller DG and ML hippocampal volumes in patients with OCD.

Although the hippocampus has been commonly studied in relation to adult neurogenesis (Shapiro et al., 2009), some evidence shows that the human amygdala may be involved in postnatal neurogenesis with cell turnover rates that are comparable to the hippocampus (Roeder et al., 2022). Rodent work indicates that the LA and BA contain immunoreactive neural cell adhesion molecules that could allow for the amygdala to participate in neuronal plasticity (Nacher et al., 2002). Additional work in rodent and non-human primates demonstrate that antidepressant-modulated neurogenesis enhances neuronal and glial cell growth in the amygdala (Bernier et al., 2002; Fowler et al., 2002). Although these findings may explain the observation of the larger amygdala BA and LA subfields in our medicated patients with OCD, it is not known whether the subfield volumetric differences observed in medicated patients in the present study reflect an innate response to medication use or neurotoxic effect of medication. Further investigation is required to elucidate the effects of medication in subcortical volumes in OCD. Another finding was that unmedicated patients with OCD had smaller hippocampal CA1 volume, compared to HCs. Although the CA1 is shown to be susceptible to stress-induced atrophy (Bartsch et
al., 2015; Kassem et al., 2013), it is unclear whether unmedicated patients experience greater stress than medicated patients with OCD, in our study. A rodent quinpirole sensitization model of OCD showed a downregulation of Arc (a marker of plasticity-related neuronal activity) expressing neurons in the CA1 during stereotypical checking behaviour suggesting that the hippocampus may be involved in OCD more than is currently thought (Brozka, 2021).

There are some limitations to consider. First, even with automated segmentation, the small size of the amygdala poses challenges in accurately identifying its borders (Saygin et al., 2011). 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 (Quattrini et al., 2020). Secondly, 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. The third limitation is the inability of our study to account for heterogeneity in the clinical presentation of OCD in our models, particularly in light of published evidence for an association between OCD symptom profile and hippocampal volume (Reess et al., 2018). Lastly, due to lack of detailed information on medication status, we were unable to further investigate the effects of medication type, dosage, and duration on subfield volumes in medicated patients with OCD.

In summary, the association of medication status with 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.
Tables and figures

Table 1A: Demographic and clinical characteristics of patients with OCD and healthy controls.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>OCD (n=381)</th>
<th>HCs (n=338)</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>SD</td>
<td>mean</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32</td>
<td>9.4</td>
<td>30.2</td>
</tr>
<tr>
<td>Education level (years)</td>
<td>13.7</td>
<td>2.8</td>
<td>14.6</td>
</tr>
<tr>
<td>Y-BOCS score mean&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25</td>
<td>6.2</td>
<td>--</td>
</tr>
<tr>
<td>Age at onset of OCD&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20.3</td>
<td>8.8</td>
<td>--</td>
</tr>
<tr>
<td>Total hippocampal volume</td>
<td>3544.4</td>
<td>340.4</td>
<td>3587.5</td>
</tr>
<tr>
<td>Total amygdala volume</td>
<td>1770.3</td>
<td>187.9</td>
<td>1783</td>
</tr>
<tr>
<td>Male</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Right-handed</td>
<td>186</td>
<td>48.8</td>
<td>179</td>
</tr>
<tr>
<td>Medication use at time of scan</td>
<td>161</td>
<td>43.6</td>
<td>--</td>
</tr>
</tbody>
</table>

<sup>a</sup> Measured by the Yale-Brown Obsessive Compulsive Scale (YBOCS) total score.  
<sup>b</sup> As measured by the Y-BOCS symptom checklist.
Table 2B: Demographic and clinical characteristics of subgroup patients with OCD.

<table>
<thead>
<tr>
<th></th>
<th>A: OCD on medication (n=161)</th>
<th>B: OCD not on medication (n=220)</th>
<th>C: OCD with anxiety (n=25)</th>
<th>D: OCD without anxiety (n=356)</th>
<th>E: OCD with MDD</th>
<th>F: OCD without MDD (n=286)</th>
<th>G: HCs</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
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<tr>
<td></td>
<td>32.89 (9.13)</td>
<td>31.33 (9.54)</td>
<td>34.48 (9.25)</td>
<td>31.81 (9.39)</td>
<td>34.99 (9.56)</td>
<td>30.99 (9.14)</td>
<td>30.2 (9.3)</td>
<td>A&gt;(G) C&gt;(G) D&gt;(G)</td>
</tr>
<tr>
<td>Education level (years)</td>
<td>12.90 (2.88)</td>
<td>14.33 (2.62)</td>
<td>14.83 (2.90)</td>
<td>13.63 (2.81)</td>
<td>13.48 (2.92)</td>
<td>13.78 (2.79)</td>
<td>14.6 (3.4)</td>
<td>A&gt;(G) D&gt;(G) E&gt;(G) F&gt;(G)</td>
</tr>
<tr>
<td>Male</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>83 (51.55)</td>
<td>103 (46.81)</td>
<td>7 (28)</td>
<td>179 (50.28)</td>
<td>32 (33.68)</td>
<td>154 (53.84)</td>
<td>179 (52.9)</td>
<td>C&gt;(G) E&gt;(G)</td>
</tr>
</tbody>
</table>

Note: mean age of OCD on medication (A), OCD with anxiety (C), OCD without anxiety (D) significantly larger than HCs (G), respectively. Years of education significantly greater in OCD on medication (A), OCD without anxiety (D), OCD with MDD (E), without MDD (F) significantly larger than HCs (G), respectively. Significantly larger number of men in OCD with anxiety (C), OCD with MDD (E) than HCs (G), respectively.
Table 3: Number of scans provided and excluded for patients with OCD and healthy controls after quality checking.

<table>
<thead>
<tr>
<th>Initial number of scans(^a)</th>
<th>Excluded for missing data</th>
<th>Excluded after visual QC</th>
<th>Reasons for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>OCD</td>
<td>HC</td>
<td>Total</td>
</tr>
<tr>
<td>Amsterdam</td>
<td>53</td>
<td>49</td>
<td>102</td>
</tr>
<tr>
<td>Barcelona</td>
<td>86</td>
<td>102</td>
<td>188</td>
</tr>
<tr>
<td>Brazil</td>
<td>58</td>
<td>40</td>
<td>98</td>
</tr>
<tr>
<td>Japan</td>
<td>88</td>
<td>48</td>
<td>136</td>
</tr>
<tr>
<td>Korea</td>
<td>87</td>
<td>97</td>
<td>184</td>
</tr>
<tr>
<td>London</td>
<td>44</td>
<td>33</td>
<td>77</td>
</tr>
<tr>
<td>Total</td>
<td>416</td>
<td>369</td>
<td>785</td>
</tr>
</tbody>
</table>

\(^a\) Reported in previous publication (De Wit et al., 2014).\(^b\) Participants excluded based on visual screening for partial or atypical segmentation using an adaptation of the ENIGMA Consortium Quality Control protocol for subcortical and hippocampal subfield (see https://enigma.ini.usc.edu/ongoing/enigma-hippocampal-subfields/). \(^c\) Participants excluded based on R script flag for abnormalities on more than 5 subfields and flagged for visual QC. \(^d\) Participants excluded based on exceeding ±5SD away from the z-standardized mean of any of the subfields.
Figure 1: Visualisation of amygdala/hippocampal Freesurfer subfield segmentation from right hemisphere of single representative healthy control, using 3DSlicer (https://www.slicer.org/). A: Lateral view, B: Medial view. The hippocampal fimbria was not included in our analysis (Brown et al., 2020).
Figure 2A: Mixed effect size estimates (d) for hippocampal and amygdala subfield volumes between patients with OCD (n=381) and healthy controls (n=338). Data presented with SE. Hippocampal subfields presented in dark blue, amygdala subfields presented in light blue. Abbreviations: cornu ammonis (CA) sectors, CA1, CA2-3, CA4, granule cell layer of dentate gyrus (DG), molecular layer (ML), hippocampus–amygdala transition area (HATA), corticoamygdaloid transition area (CAT), anterior amygdaloid area (AAA).
**Figure 2B:** Mixed effect size estimates (d) for hippocampal and amygdala subfield volumes between *medicated patients with OCD* (n=161) and healthy controls (n=291). Data presented with SE, (*) Denotes significant difference *p*<0.05. Hippocampal subfields presented in dark blue, amygdala subfields presented in light blue. Abbreviations: cornu ammonis (CA) sectors, CA1, CA2-3, CA4, granule cell layer of dentate gyrus (DG), molecular layer (ML), hippocampus–amygdala transition area (HATA), corticoamygdaloid transition area (CAT), anterior amygdaloid area (AAA).
Table 4: Mixed effect size estimates (d), SE, uncorrected and corrected (FDR) p-value for hippocampal and amygdala subfield volumes between patients with OCD (n=381) and healthy controls (n=338).

<table>
<thead>
<tr>
<th>Hippocampal subfields</th>
<th>Effect size (mixed-effects d)</th>
<th>Standard Error (SE)</th>
<th>P value (uncorrected)</th>
<th>P value (corrected (p_{FDR}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasubiculum</td>
<td>0.051</td>
<td>0.075</td>
<td>0.443</td>
<td>0.664</td>
</tr>
<tr>
<td>Presubiculum</td>
<td>0.152</td>
<td>0.075</td>
<td>0.037</td>
<td>0.156</td>
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<tr>
<td>Subiculum</td>
<td>0.039</td>
<td>0.075</td>
<td>0.540</td>
<td>0.756</td>
</tr>
<tr>
<td>CA1</td>
<td>-0.196</td>
<td>0.075</td>
<td>0.006</td>
<td>0.063</td>
</tr>
<tr>
<td>CA3</td>
<td>-0.096</td>
<td>0.075</td>
<td>0.164</td>
<td>0.353</td>
</tr>
<tr>
<td>CA4</td>
<td>-0.111</td>
<td>0.075</td>
<td>0.104</td>
<td>0.353</td>
</tr>
<tr>
<td>DG</td>
<td>-0.155</td>
<td>0.075</td>
<td>0.023</td>
<td>0.150</td>
</tr>
<tr>
<td>ML</td>
<td>-0.207</td>
<td>0.075</td>
<td>0.003</td>
<td>0.060</td>
</tr>
<tr>
<td>HATA</td>
<td>-0.049</td>
<td>0.075</td>
<td>0.363</td>
<td>0.636</td>
</tr>
<tr>
<td>fimbria</td>
<td>0.108</td>
<td>0.075</td>
<td>0.122</td>
<td>0.353</td>
</tr>
<tr>
<td>Hippocampal fissure</td>
<td>0.012</td>
<td>0.075</td>
<td>0.864</td>
<td>0.955</td>
</tr>
<tr>
<td>Hippocampal tail</td>
<td>0.030</td>
<td>0.075</td>
<td>0.681</td>
<td>0.841</td>
</tr>
<tr>
<td>Amygdala subfields</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral nucleus</td>
<td>0.095</td>
<td>0.075</td>
<td>0.168</td>
<td>0.353</td>
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<tr>
<td>Basal nucleus</td>
<td>0.102</td>
<td>0.075</td>
<td>0.149</td>
<td>0.353</td>
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<tr>
<td>Accessory basal nucleus</td>
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<td>0.075</td>
<td>0.802</td>
<td>0.935</td>
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<tr>
<td>Central nucleus</td>
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<td>0.075</td>
<td>0.631</td>
<td>0.828</td>
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<tr>
<td>Medial nucleus</td>
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<td>0.075</td>
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<tr>
<td>Cortical nucleus</td>
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<td>0.075</td>
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<td>0.979</td>
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<tr>
<td>Paralaminar nucleus</td>
<td>0.154</td>
<td>0.075</td>
<td>0.029</td>
<td>0.150</td>
</tr>
<tr>
<td>CAT</td>
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<td>0.979</td>
<td>0.979</td>
</tr>
<tr>
<td>AAA</td>
<td>-0.050</td>
<td>0.075</td>
<td>0.419</td>
<td>0.664</td>
</tr>
</tbody>
</table>

Abbreviations: cornu ammonis (CA) sectors, CA1, CA2-3, CA4, granule cell layer of dentate gyrus (DG), molecular layer (ML), hippocampus–amygdala transition area (HATA), corticoamygdaloid transition area (CAT), anterior amygdaloid area (AAA). P-values are presented before and after correction for multiple comparison using the false discovery rate (FDR). Data presented with SE.
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