Distinguishing Between Major Depressive Disorder and Obsessive-Compulsive Disorder in Children by Measuring Regional Cortical Thickness

Erin Fallucca, MD1,2, Frank P. MacMaster, PhD1,3, Joseph Haddad, BS1, Phillip Easter, BA1, Rachel Dick, BA1, Geoffrey May, BS1, Jeffrey A Stanley, PhD1, Carrie Rix, BS1, and David R. Rosenberg, MD1

1Department of Psychiatry & Behavioral Neurosciences, Wayne State University, and Children’s Hospital of Michigan, Detroit, MI 48201
2Department of Psychiatry and Behavioral Neurosciences, George Washington University, Washington, DC 20037
3Departments of Psychiatry and Pediatrics, University of Calgary, Calgary, AB T3B 6A8

Abstract

Context—Cortical abnormalities have been noted in previous studies of major depressive disorder (MDD).

Objective—We hypothesized differences in regional cortical thickness in children with MDD, with obsessive-compulsive disorder (OCD) and healthy controls.

Design—Cross-sectional examination of the groups.

Setting—Children’s Hospital of Michigan.

Patients or Other Participants—Twenty-four psychotropic drug-naïve pediatric MDD patients (9 males, 15 females), twenty-four psychotropic drug-naïve pediatric outpatients with OCD (8 males, 16 females) and thirty healthy pediatric controls (10 males, 20 females).

Intervention—Subjects underwent magnetic resonance imaging (MRI).

Main Outcome Measure—Cortical thickness.

Results—In the right hemisphere, the pericalcarine (p = 0.002, p = 0.04), post central (p = 0.002, p = 0.02) and superior parietal gyri (p = 0.008, p = 0.03) were thinner in MDD compared to both OCD and controls subjects respectively. OCD and control subjects did not differ in these regions. The temporal pole was thicker in MDD patients than both OCD patients (p = 0.0007) and controls (p = 0.01), which did not differ. The cuneus was thinner in MDD patients compared to OCD patients (p = 0.008), but did not differ from controls. In the left hemisphere, the supramarginal gyrus was comparably thinner in both MDD (p = 0.04) and OCD (p = 0.01) than in controls, and
the temporal pole was thicker in MDD patients than in both controls and OCD patients, \( p = 0.0009 \).

**Conclusions**—To our knowledge, this is the first study to explore cortical thickness in pediatric MDD patients. While differences in some regions would be expected given neurobiological models of MDD, this study highlights some unexpected regions (i.e. supramarginal, superior parietal) that merit further investigation. These results underscore the need to expand exploration beyond the frontal-limbic circuit.

**Keywords**

Adolescents; Children; Cortical Thickness; Depression; Magnetic Resonance Imaging; Obsessive-Compulsive Disorder

**Introduction**

Major depressive disorder (MDD) is a common, debilitating illness with frequent onset in childhood and adolescence. MDD has a lifetime prevalence of approximately 5% in adolescence and is believed to be continuous with adult MDD \(^1\), \(^2\). Studies of pediatric patients with MDD may minimize potential confounds, such as treatment intervention and illness duration.

Abnormalities in frontal \(^3\), \(^4\), limbic \(^5\)-\(^12\) and hypothalamic-pituitary-adrenal (HPA) axis \(^13\)-\(^15\) structures have been implicated in MDD. In a study of the cytoarchitecture of the left rostral and caudal orbitofrontal and dorsolateral prefrontal cortical regions in subjects with major depression as compared to psychiatrically normal controls, Rajkowska et al \(^16\) found decreases in cortical thickness, neuronal sizes and neuronal and glial densities in the upper (II-IV) cortical layers of the rostral orbitofrontal region in MDD patients. In the caudal orbitofrontal cortex in MDD subjects, prominent reductions in glial densities in the lower (V-VI) cortical layers were accompanied by small, but significant decreases in neuronal sizes. In the dorsolateral prefrontal cortex of MDD subjects, reductions in the density and size of neurons and glial cells were found in both supra- and infragranular layers. Family history may influence the underlying neurobiology of MDD \(^3\), \(^4\), \(^6\), \(^17\), \(^18\). Recently, Peterson et al \(^19\) suggested that cortical thinning in the right hemisphere produces disturbances in arousal, attention and memory for social stimuli, which in turn may increase the risk of developing depressive illness in those at high risk – via family history – for MDD.

The identification of relevant biomarkers in MDD is a major aim of research into the neurobiology of the illness. Previous work found compelling differences between thalamic neurochemistry in patients with obsessive-compulsive disorder (OCD) and MDD \(^20\), \(^21\); and areas of similarity, like anterior cingulate neurochemistry \(^22\). A sensitive and specific biomarker would enhance our understanding of the pathophysiology of MDD and may help to define the phenotype and reduce heterogeneity in genetic studies and facilitate early detection and intervention. An ideal biomarker for MDD would have high sensitivity and specificity for the disorder in affected patients. The diagnostic specificity of abnormalities in cortical thickness, however, has not been widely studied.
Two-thirds of OCD patients will develop depression during their lifetime. Prior functional imaging studies in adult and pediatric patients with OCD and MDD have demonstrated comparable findings in some regions and distinct findings in others\textsuperscript{20-23}. One important area of research is to determine if neurobiologic findings are specific to a particular psychiatric diagnosis or generalizes across diagnoses, so we have also included a group of patients with OCD to serve as a psychiatric control group. In this study, we chose to measure cortical thickness in psychotropic naive children with MDD, OCD and healthy controls. This method employs a surface based measurement approach which, unlike voxel based morphometry (VBM), is able to interpret folding across the entire cortex\textsuperscript{24}. Freesurfer’s cortical thickness measurement technique has been previously validated using postmortem studies and is able to accurately detect sub-millimeter variations in gray matter\textsuperscript{24}. Based on previous studies of pediatric MDD and OCD, we hypothesized significant differences in cortical thickness would exist in the anterior cingulate, orbital frontal cortex and dorsolateral prefrontal cortex (DLPFC) regions. We examined for laterality effects since several of our previously published neuroimaging studies found striking laterality effects for both volumetric and neurochemical measures in pediatric patients with MDD\textsuperscript{3, 4}. Given prior investigation suggesting distinct alterations in familial vs. non-familial MDD\textsuperscript{3, 4, 6, 17, 18}, we also conducted an exploratory analysis of the effect of familial vs. non-familial MDD on cortical thickness.

**Subjects and Methods**

**Subjects**

Twenty-four psychotropic drug-naïve pediatric outpatients with MDD (mean ± standard deviation unless otherwise stated: 13.96 ± 2.41 years; 9 males, 15 females) and twenty-four psychotropic drug-naïve pediatric outpatients with OCD (as a psychiatric control group, 13.02 ± 2.92 years; 8 males, 16 females) were included in this study (see table 1). In the MDD group, 15 subjects had at least one first degree relative with MDD. Thirty control participants (13.44 ± 2.78 years; 10 males, 20 females) were used as a comparison group. All patients were recruited through the Wayne State University child psychiatry outpatient clinic. Diagnoses were made using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Versions (K-SADS-PL)\textsuperscript{25}. A board certified child and adolescent psychiatrist (D.R.R.), interviewed each subject and their parents to confirm the presence of DSM-IV criteria for OCD or MDD.

Fifteen of 24 MDD patients exhibited comorbid disorders, including attention deficit disorder without hyperactivity, oppositional defiant disorder and anxiety disorders, including generalized anxiety disorder and separation anxiety disorder. Three of the MDD patients who had comorbid attention deficit disorder without hyperactivity had not been previously treated with stimulant medication or other pharmacotherapy for ADHD. Nine of the 24 MDD patients had MDD as their sole diagnosis. Eleven of the 15 MDD patients with at least one first degree relative with MDD and four of the nine MDD patients with no obvious family history of MDD had comorbid disorders. Nine of the 24 OCD patients exhibited comorbid disorders, including dysthymia, anxiety disorders, enuresis, oppositional defiant disorder, and seasonal affective disorder. 15 had OCD as their sole diagnosis. Exclusion
criteria for both patients and healthy controls included a lifetime history of bipolar disorder, psychosis, eating disorders, Sydenham's chorea, conduct disorder, substance abuse or dependence, Tourette's syndrome, pervasive developmental disorders, mental retardation, learning disorders or significantly debilitating medical and neurological conditions. OCD patients did not have a lifetime history of MDD and MDD patients did not have a lifetime history of OCD nor sub-threshold obsessive compulsive symptoms and behaviors. There was no history of psychiatric illness in the healthy controls or in any of their first-degree relatives. The parents, as well as the children, served as informants for these diagnostic assessments. After complete description of the study to the subjects, written informed consent was obtained from the legal guardian and the participants provided written assent. The Wayne State University Human Investigation Committee provided approval to conduct this project.

Clinical Assessments

Measures of depression and anxiety were obtained using the 17-item Hamilton Depression Rating Scale (MDD patients: 17.00 ± 7.65; OCD patients: 7.13 ± 6.33) \(^26\) and the Hamilton Anxiety Rating Scale (MDD patients: 12.24 ± 5.07; OCD patients: 7.04 ± 5.76) \(^27\) respectively. The Ham-D and Ham-A were used to ascertain depression and anxiety for consistency of measurement across diagnoses. The Children's Yale-Brown Obsessive Compulsive Scale was used to assess the OCD symptom severity in OCD patients (24.21 ± 7.00) \(^28\). Duration of illness was 24.90 ± 31.32 months and 41.17 ± 39.75 months in the MDD patients and OCD patients respectively.

MRI Procedures

MRI examinations were conducted at the Children's Hospital of Michigan Imaging Center. The imaging acquisition methods have been described previously in detail \(^29, 30\). All images were acquired in the coronal plane after performing a sagittal scout series to verify patient position, cooperation and image quality. The sequence was produced using a three-dimensional spoiled gradient echo pulse sequence with a 40 degree flip angle, 25-msec repetition time and a 5-msec echo time on a 1.5 T whole-body superconducting imaging system (General Electric, Milwaukee). One hundred and twenty-four contiguous coronal slices (slice thickness=1.5 mm, no gap) were produced through the whole brain using this sequence. The in-plane resolution produced was 0.94×0.94 mm in a 256×256 matrix. Axial proton density and T2-weighted images were obtained to exclude structural abnormalities. A pediatric neuroradiologist reviewed all scans to rule out clinically significant abnormalities.

Image Analysis

Cortical reconstruction and volumetric segmentation was performed with the automated FreeSurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures have been described in detail previously \(^24\). FreeSurfer uses a cortical surface model based on probabilistic information estimated from a manually labeled training set to create cortical sulci and gyri parcellations. This procedure, which incorporates geometric information derived from the cortical model, and neuroanatomical convention, as defined by the training set, has been described previously \(^31, 32\). Briefly, after the application of intensity variations...
to correct magnetic field inhomogeneities, non-brain voxels from each subject's T1-weighted MRI were removed and then these images were segmented using an estimation of the gray-white interface. Each scan was inflated to create a smooth spherical surface in order to reduce interference created by folds in the cortical mantle and was registered to a spherical surface representation reference template that was created from an averaged pattern of a group of representative subjects and is the default template provided by FreeSurfer. Alignment of the spherical surface of the reconstructed brains to the reference template was achieved through a 2-D warp of the subject's sphere surface that aligned the sulcal and gyral features of each subject to the curvature data pattern of the template, ensuring optimal alignment across subjects. Next, a circularly symmetric Gaussian kernel was used to smooth the maps and averaging across subjects was performed to align cortical folding patterns. Average measures of cortical thickness were produced at each point on the reconstructed surface. The spherical transform was used to map the thickness measurements at each vertex on each subject's cortical surface into a common spherical coordinate system. The data were smoothed on the surface tessellation using an iterative nearest-neighbor averaging procedure (50 iterations were applied, equivalent to applying a two-dimensional Gaussian smoothing kernel along the cortical surface with a full-width/height maximum of 13 mm) and a deformable surface algorithm was used to define the pial surface with sub-millimeter accuracy. Data were then re-sampled for participants into a common spherical coordinate system. Manual corrections to the segmentation were then made to each cortex. These procedures were carried out by an investigator who was blinded to subject group assignment. Thickness across the cortex was measured by averaging each point between the gray-white boundary surface and the estimated pial surface. Validation of this technique has been confirmed by direct comparisons with manual measures on postmortem brains, as well as direct comparisons with manual measures on MRI data.

**Statistical Analysis**

All statistical analyses were conducted using the IBM Statistical Package for Social Sciences (V18.0). An analysis of covariance (ANCOVA) was used to compare the three groups using age as a covariate. Post-hoc analysis used least significant differences (LSD) tests. There were 31 comparisons (.05/31 = .002) and alpha was set at p < 0.002. Age was selected as a covariate given the wide age range and likelihood of regions of interest correlating with age. Sex was also used as a covariate in order to accommodate possible gender effects. Pearson correlations were used to examine the relationship between significant differences in cortical thickness and clinical variables. In an exploratory manner, a sub-analysis comparing familial MDD, non-familial MDD, OCD and controls was also conducted - as this is an exploratory sub-analysis, alpha was set at 0.05.

**Results**

**Right Hemisphere**

In the right hemisphere, the pericalcarine, post central and superior parietal gyrus were thinner in MDD compared to both OCD and control subjects, with no difference between OCD and controls (Figure 1). The temporal pole was thicker in MDD patients than both...
OCD patients and controls. Interestingly, the cuneus was thinner in MDD patients as compared to OCD patients, with a trend to be thinner than controls. In the cuneus, OCD patients also demonstrated a trend to be thicker than controls (see table 2).

Left Hemisphere

The supramarginal gyrus tended to be thinner in both MDD and OCD than in controls although the threshold of p = .002 was not quite met (Figure 1). The temporal pole was thicker in MDD patients than in both controls and OCD patients (Table 2).

Demographic and Clinical Correlations

In MDD patients, an association with age of onset of illness was seen (r = -0.516, p = 0.012) with the left supramarginal gyrus. Right temporal pole correlated negatively with Ham-D in MDD patients (r = -0.450, p = 0.031). No other correlations with clinical variables were significant.

Exploratory Analysis – The Effect of Family History of Mood Disorder

The effect of cortical thickness variations observed in MDD subjects was driven by subjects with familial history of MDD. The right post central gyrus and right superior parietal gyrus were thinner in familial MDD subjects compared to control subjects (p = 0.01; p = 0.03 respectively) and OCD subjects (p = 0.002; p = 0.001 respectively), with no difference between OCD and controls. Similarly, the left supramarginal gyrus was also thinner in familial MDD subjects compared to control subjects (p = 0.04), but was also thinner in OCD subjects compared to control subjects (p = 0.01). Both the right and left temporal poles were also thicker in familial MDD subjects compared to control subjects (p = 0.02; p = 0.009 respectively) and OCD subjects (p = 0.002; p = 0.0001 respectively), with no difference between OCD and controls (see online Supplementary Table).

Discussion

To our knowledge, this is the first study to use the automated FreeSurfer technique in order to explore cortical thickness in pediatric MDD and OCD patients. In MDD patients, decreased cortical thickness was observed in the left supramarginal gyrus, right pericalcarine gyrus, post-central gyrus, superior parietal lobule and cuneus. Greater thickness in bilateral temporal pole was noted. In OCD patients, the only significantly different region from controls was a thinner left supramarginal gyrus. Our findings in the study of cortical thickness were unexpected as no significant differences were found in the anterior cingulate, DLPFC or orbital frontal cortex in MDD or OCD patients. This lack of patient group differences in hypothesized regions (anterior cingulate, orbital frontal cortex and dorsal prefrontal cortex) could possibly be due to Type II error. However, it should be noted that types of errors introduced are not limited to only Type II based on significance level choices, but also limitations in specific cortical regions, proximity to subcortical gray matter structures and cortical folding patterns 36-38. Additionally, the process of subdividing our sample into four comparison groups (i.e. Controls, Familial MDD, Non-familial MDD and OCD) will have weakened the statistical power and the ability to detect differences. It is also possible that this may be due to the relatively small sample size or limitations in method
such as our use of the standard template provided by freesurfer rather than a pediatric template that would have been more closely representative of our sample. Although use of an adult template was not expected to have had much of an effect for the age range examined in this study, the choice of template for segmentation could have resulted in possible bias related to adult vs. an age appropriate atlas. The sample was, however, unique in that all MDD and OCD patients were psychotropic-naïve. These findings also underscore the need to look beyond standard frontal-limbic (MDD) and frontal striatal (OCD) models in these disorders.

Findings in the right post central gyrus, superior parietal lobule, left supramarginal gyrus and bilateral temporal pole appear to be driven by familial MDD subjects. The findings in the right hemisphere are consistent with Peterson et al. who found cortical thinning in the right hemisphere in subjects with no personal history of MDD who were at increased risk for developing MDD. Our investigation extends these results by finding differences in affected pediatric MDD patients as compared to a psychiatric comparison group of pediatric OCD patient. While speculative, cortical thinning effects may be stronger for familial than nonfamilial depression due to environmental and genetic factors. There may be a protective factor in pediatric nonfamilial MDD patients who may be in an environment in which they can better cope with their illness.

Possibly consistent with our finding of thinner post central gyrus in MDD, lower regional cerebral blood flow has been noted in the post-central gyrus in MDD patients. In a group at high risk for depression, abnormal activation of the superior parietal lobule was noted as compared to low-risk controls. Cognitive changes with MDD, like impaired sustained attention, may be associated with parietal dysfunction. Abnormal glucose metabolism was also noted in MDD patients in the cuneus as compared to controls. Although we found the temporal pole to be thicker in MDD patients than controls, no volumetric differences have been noted previously. Greater activation in the temporal pole has been noted in MDD patients trying to voluntarily down-regulate sad feelings. In 12 severely depressed subjects, Keedwell et al. found that depression severity correlated positively with responses to sad stimuli in temporal pole. Lower grey matter density has also been noted with VBM studies of the temporal pole in first episode MDD, although negative findings do exist. The temporal pole has connections to orbital and medial prefrontal regions, areas commonly implicated in MDD. The supramarginal gyri have not been previously implicated in the pathogenesis of MDD. The effects noted in the right superior parietal lobule, post-central gyrus, supramarginal gyrus and bilateral temporal poles were also driven by familial MDD primarily, akin to previous findings in the hippocampus in pediatric MDD.

The cortical thinning found in the left supramarginal gyrus was the only significant difference noted between OCD patients and controls. It has been hypothesized that the repetitive behaviors of OCD reflect problems in set shifting and the supramarginal gyrus plays a role in set shifting. Interestingly, the supramarginal gyrus and parietal lobe in general, have been implicated in OCD previously, but their role in the disorder remains little explored.
More critically, cortical thickness distinguished psychotropic naïve pediatric MDD patients from both psychotropic-naive pediatric OCD patients and healthy controls in several regions. This builds on prior work in pediatric OCD and MDD which has demonstrated distinct functional and neurochemical alterations in some, but not all, regions of interest. These results also suggest that alterations in cortical thickness may be more prominent in familial than in non-familial MDD patients. Some of the regions identified have also been identified to be thinner in premature infants as children. According to history reports obtained during our assessments, all subjects were of normal gestational age and had no in utero exposure. However, more sophisticated interviews and history are likely necessary for the best assessment of this. Comorbidity also differed between MDD and OCD patients. The cortical thinning found in MDD patients but not in OCD patients and controls could be confounded by comorbid disorders, e.g., ADHD in MDD but not OCD patients. We also ran ancillary analyses where we excluded MDD patients with comorbid anxiety disorders and non-depressed OCD patients with dysthymia and high levels of depressive symptoms on the HAM-D since it is possible that overlap in depression/anxiety diagnoses might preclude our ability to see MDD vs. OCD group differences in frontal and other regions. However, comparable results were observed with these ancillary analyses underscoring the need for further study in larger samples.

This study did not produce the expected results in this sample of pediatric MDD and OCD patients. No significant abnormalities were found in the frontal lobe structures. However, changes in parietal and temporal cortex were observed. This highlights the need to expand our exploration of brain regions from the typical standard regions of interest. Further exploration to determine whether these findings are reproducible in larger and independent samples of MDD and OCD patients is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References


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Figure 1.
Cortical thickness results for the right superior parietal gyrus and the left supramarginal gyrus. MDD = major depressive disorder, OCD = Obsessive-Compulsive Disorder.
# Table 1  
**Demographic information**

<table>
<thead>
<tr>
<th>Item</th>
<th>Healthy Comparison Subjects (n = 30)</th>
<th>Major Depressive Disorder Patients (n = 24)</th>
<th>Obsessive Compulsive Disorder Patients (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>14.11 ± 2.57</td>
<td>13.96 ± 2.41</td>
<td>13.02 ± 2.92</td>
</tr>
<tr>
<td>Age Range (years)</td>
<td>9.08 – 18.82</td>
<td>7.98 – 17.28</td>
<td>8.24 – 18.71</td>
</tr>
<tr>
<td>Gender</td>
<td>10 males, 20 females</td>
<td>9 males, 15 females</td>
<td>8 males, 16 females</td>
</tr>
<tr>
<td>Duration of Illness (months)</td>
<td>-</td>
<td>24.90 ± 31.32</td>
<td>41.17 ± 39.75</td>
</tr>
<tr>
<td>Hamilton Depression</td>
<td>-</td>
<td>17.00 ± 7.65</td>
<td>7.13 ± 6.33</td>
</tr>
<tr>
<td>Hamilton Anxiety</td>
<td>-</td>
<td>12.24 ± 5.07</td>
<td>7.04 ± 5.76</td>
</tr>
<tr>
<td>CY-BOCS</td>
<td>2.14 ± 2.85</td>
<td>-</td>
<td>24.21 ± 7.00</td>
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</tbody>
</table>

Data are given as mean ± standard deviation
Cortical Thickness Results of Three Group Comparison

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Healthy Comparison Subjects (n = 30)</th>
<th>Major Depressive Disorder Patients (n = 24)</th>
<th>Obsessive Compulsive Disorder Patients (n = 24)</th>
<th>F Value</th>
<th>P Value</th>
<th>HC/MDD</th>
<th>HC/OCD</th>
<th>MDD/OCD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Pericak-carine Gyrus</td>
<td>1.847 ± .205</td>
<td>1.722 ± .132</td>
<td>1.926 ± .329</td>
<td>8.09</td>
<td>&lt;.001</td>
<td>.04</td>
<td>n.s.</td>
<td>.002</td>
</tr>
<tr>
<td>Right Postcentral Gyrus</td>
<td>2.408 ± .391</td>
<td>2.184 ± .171</td>
<td>2.495 ± .417</td>
<td>6.94</td>
<td>.002</td>
<td>.02</td>
<td>n.s.</td>
<td>.002</td>
</tr>
<tr>
<td>Right Superior Parietal Gyrus</td>
<td>2.560 ± .318</td>
<td>2.387 ± .224</td>
<td>2.676 ± .380</td>
<td>7.33</td>
<td>.001</td>
<td>.03</td>
<td>n.s.</td>
<td>.008</td>
</tr>
<tr>
<td>Right Temporal Pole</td>
<td>3.655 ± .773</td>
<td>4.092 ± .316</td>
<td>3.446 ± .676</td>
<td>8.06</td>
<td>&lt;.001</td>
<td>.01</td>
<td>n.s.</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Right Cuneus</td>
<td>2.306 ± .448</td>
<td>2.083 ± .187</td>
<td>2.511 ± .585</td>
<td>8.35</td>
<td>&lt;.001</td>
<td>.06</td>
<td>.06</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Left Supramarginal Gyrus</td>
<td>3.009 ± .457</td>
<td>2.843 ± .201</td>
<td>2.800 ± .281</td>
<td>6.41</td>
<td>.003</td>
<td>.04</td>
<td>.01</td>
<td>n.s.</td>
</tr>
<tr>
<td>Left Temporal Pole</td>
<td>3.586 ± .657</td>
<td>4.012 ± .319</td>
<td>3.322 ± .663</td>
<td>7.73</td>
<td>&lt;.001</td>
<td>.005</td>
<td>n.s.</td>
<td>&lt;.001</td>
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</table>

Data are given as mean ± standard deviation