Grey matter morphology in women with premenstrual dysphoric disorder treated with a selective progesterone receptor modulator

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Abstract
Premenstrual dysphoric disorder (PMDD) is characterized by severe cyclic mood symptoms emerging in the luteal phase of the menstrual cycle. The variation in progesterone levels and its metabolites during the luteal phase seems critical to the occurrence of PMDD symptoms. Notably, the efficacy of selective progesterone receptor modulator (SPRM) treatment on the mental symptoms of PMDD has been recently demonstrated. In the present study, structural magnetic resonance imaging was used to assess the effects of SPRM treatment, compared with placebo, on grey matter morphology in women with PMDD. In total, 35 women were scanned during the luteal phase, before and after three months of treatment with SPRM or placebo. Symptom severity was assessed using the Daily Record of Severity of Problems (DRSP), while gonadal hormone levels were measured by liquid chromatography-tandem mass spectrometry. Region-of-interest and whole-brain approaches were employed to perform voxel-based morphometry analyses, subcortical volumetric analyses, and surface-based morphometry analyses. No interaction or main effects of treatment and time were observed on grey matter volume and...
cortical surface measures (cortical thickness, gyration index, sulcal depth, and fractal dimension). The relationship between change in brain morphology and symptom severity was also explored but no treatment-dependant grey matter structure change was related to symptom severity change. These findings suggest that SPRM treatment does not impart macrostructural changes onto grey matter structure, at least in the short term.

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1. Introduction

About 5% of women during their reproductive age suffer from premenstrual dysphoric disorder (PMDD), a sex-specific mood disorder entailing debilitating affective and physical symptoms that impair everyday functioning (Epperson et al., 2012). Even though symptoms coincide with sex hormone fluctuations in the luteal phase, women with PMDD have similar progesterone and oestradiol levels as healthy women (Bäckström et al., 2003; Epperson et al., 2012). Notably, stable and low levels of these hormones are associated with beneficial mental outcomes in PMDD (Schmidt et al., 2017). Thus, maladaptive neural response to progesterone and oestradiol fluctuations during ovulatory cycles is suggested to induce PMDD symptomatology (Comasco and Sundström-Poromaa, 2015).

Low-dose selective progesterone receptor modulator (SPRM) administration, via antagonistic effects on the progesterone receptor, induces anovulation in most women, leading to low progesterone levels (Rabe et al., 2018), while oestradiol is kept at mid-follicular levels (Whitaker et al., 2014). Recently, we demonstrated the clinical efficacy of three-month low-dose SPRM treatment on mental symptoms in PMDD, especially depression and irritability (Comasco et al., 2021). Additionally, in a recent functional neuroimaging study, we found an association between SPRM treatment and differential fronto-cingulate reactivity during aggressive responding to provocation as compared to the baseline condition (Kaltsoni et al., 2021). The reactive aggression task entails winning, stealing or protecting points against a fictitious opponent that is sporadically provoking subjects by stealing their acquired points (Kose et al., 2015). Greater dorsal cingulate and dorsomedial prefrontal activation during aggressive response to provocation was observed in women with PMDD who were treated with SPRM in comparison with placebo (Kaltsoni et al., 2021), suggesting improved top-down regulation. However, whether such effect of SPRM treatment on brain activity entails structural neural changes remains to be determined, as well as the association between variation in brain structure and symptom change.

Progesterone and oestrogen receptors are expressed in brain areas relevant to cognitive and emotional processing (Barth et al., 2015). The highest concentration in progesterone levels have been found in the amygdala, nucleus accumbens, hypothalamus, and cerebellum, as demonstrated by post-mortem studies (Bixo et al., 1997). In rodents, progesterone can affect dentritic spine density in hippocampal CA1 pyramidal cells or cerebellar Purkinje cells (Sakamoto et al., 2002; Woolley and McEwen, 1993). In healthy individuals, neuroimaging studies have reported menstrual cycle-dependant changes in grey matter structure, in a series of regions including frontal, parietal and limbic areas (Dubol et al., 2021). In line, progesterone levels have been bidirectionally related to grey matter volume (GMV) in several regions, including the hippocampus, the cerebellum, basal ganglia, amygdala, and anterior cingulate cortex (Dubol et al., 2021). Moreover, in naturally cycling women, lateral orbitofrontal cortical thickness was thinner in women in the progesterone-dominated luteal phase compared with the follicular phase (Petersen et al., 2015). Thus, it is likely that SPRM treatment has the potential to impact on grey matter structure.

In PMDD, functional neuroimaging studies have primarily provided evidence on the relationship between progesterone levels and functional reactivity in emotion and cognitive processing regions (Dubol et al., 2020). Progesterone has been associated with differential activity in regions responsible for mood regulation, such as frontal and limbic regions, during emotional tasks (Dubol et al., 2020), where progesterone receptors have also been documented to be highly expressed (Barth et al., 2015). There are only few studies on GMV in PMDD, mainly comparing patients vs. controls, and showing inconsistent and mostly negative results (Dubol et al., 2020). Recently, we demonstrated a negative relationship between bilateral amygdala GMV and various PMDD symptoms related to depression during the luteal phase (Dubol et al., 2022b). As for brain surface measures, one study investigating the cortical thickness in women with PMDD and controls, yielded negative results (Syan et al., 2018), while recent findings indicate several bidirectional relationships between both mental and physical PMDD symptoms and four different surface architecture indices (cortical thickness, gyration index, sulcal depth, cortical complexity) for frontal and parahippocampal regions (Dubol et al., 2022b). Furthermore, we demonstrated that grey matter volume is a potential neuroanatomical signature of PMDD, as indicated by data-driven classification of women with PMDD compared with healthy controls based on structural MRI (Dubol et al., 2022a). However, to the best of our knowledge, the neural signatures of treatment effects on PMDD or correlates related to PMDD symptoms relief have yet to be investigated. Since neuroanatomical alterations are associated with the pathophysiology of other more considerably studied mood disorders (Bora et al., 2010; Kempston et al., 2011; Schmaal et al., 2016), and grey matter changes have been linked to treatment response to different interventions (Chen et al., 2007; Joshi et al., 2016), we hypothesized that structural changes are part of the potential effects of SPRM treatment.
Here, voxel- (VBM) and surface- based morphometry (SBM) were employed to assess grey matter volume and surface morphology, respectively. In women with PMDD treated with DRSP or placebo. The VBM approach assesses the GMV and allows the quantification of regional differences across subjects (Ashburner and Friston, 2000), while the SBM methodology provides more insights on cortical architecture by assessing the surface parameters of cortical thickness, gyriﬁcation, sulcal depth, and fractal dimension (Gaser and Dahmke, 2016). Cortical thickness is a measure relevant to the number of cortical neurons in the radial cortical columns (Rakic, 2009), while all measures of gyriﬁcation, sulcal depth, and fractal dimension provide information about cortical folding (Luders et al., 2006), which is associated with radial neuronal migration due to the tension caused by neuronal connections (White et al., 2010).

In line with the hypothesis that PMDD is related to impaired top-down control on limbic response to emotional stimuli (Dubol et al., 2020), SPRM treatment was hypothesized to be associated with grey matter changes in cortical and subcortical regions of relevance to PMDD. Thus, the aim of the current study was to explore the effect of SPRM on grey matter morphology in women with PMDD and the relationship with change in symptom severity. To this end, GMV and cortical surface metrics were compared over time between women treated with SPRM and placebo.

Due to limited and inconsistent literature on the structural brain correlates of PMDD (Dubol et al., 2020), no directional hypotheses on the effect of SPRM treatment on grey matter could be posited. Likewise, because of the lack of a consistently demonstrated neurocircuitry involved in PMDD (Dubol et al., 2020), we employed both a region of interest (ROI), as well as a conservative whole-brain analysis based approach to investigate the grey matter correlates of SPRM treatment. Regarding the relationship between structural alterations and symptom change, a ROI analysis approach was employed, targeting regions that have been reported to be implicated in PMDD (Dubol et al., 2020).

2. Experimental procedures

2.1. Participants

The present pharmacological imaging study was part of a double-blind, randomized, placebo-controlled clinical trial (Comasco et al., 2021), approved by the ethics committee of Uppsala (Dnr. 2016/184). The CONSORT diagram of the present study is presented in Figure S1. Thirty-six women with a diagnosis of PMDD and aged 18-46 years were recruited for this study. Diagnosis was confirmed by use of the Daily Report Severity of Problems (DRSP) scale (Endicott et al., 2006) during two consecutive cycles. Women qualifying for a PMDD diagnosis were required to have marked premenstrual symptoms and present > 50% increase from the follicular phase (days 6 - 12) to the luteal phase (days -7 to −1) of the cycle in at least five out of eleven symptoms. At least one out of five had to be a core PMDD symptom (depressive symptoms, affective lability, irritability/anger, anxiety). Percent increase in symptoms was calculated based on the following formula [(mean luteal phase scores - mean follicular phase scores) / mean follicular phase scores] x 100. It was additionally required that the luteal symptoms had to be at least mild (mean luteal phase score > 3.0), with at least two days with scores ≥ 4, and disappeared during the follicular phase (mean follicular phase score < 2.0). Exclusion criteria included presence of ongoing psychiatric disorders (using the Mini-International Neuropsychiatric interview (Sheehan et al., 1998)), contraindication to magnetic resonance imaging, irregular menstrual cycles, oral contraceptive use, pregnancy, psychotropic drug use during the past three months, and other severe medical conditions. Blood serum concentrations of progesterone and oestradiol were assessed to confirm menstrual cycle phase.

Regarding PMDD diagnosis and symptom recording throughout the treatment months, the DRSP scale was filled out by the participants on a daily basis through a smartphone application, as described in (Comasco et al., 2021). The DRSP is a 21-item scale assessing premenstrual physical and psychological symptoms, using a 6-point severity scale for scoring (Endicott et al., 2006). The total DRSP score was computed through the sum of all items, while the four subscales were computed as the sum of the items corresponding to the core PMDD symptoms as defined by the DSM-5, namely the DRSP irritability (items: anger and/ or irritability and conflicts with people), DRSP depression (items: felt depressed, felt hopeless, felt worthless or guilty), DRSP affective lability (items: had mood swings, was more easily hurt), and DRSP anxiety (items: felt more anxious) subscales (Eisenlohr-Moul et al., 2017). One woman receiving SPRM treatment was excluded from the neuroanatomical analyses due to technical issues, which resulted in 35 women (18 randomized to SPRM and 17 to placebo treatment) being included in the analyses. Treatment remission status were evaluated as described in (Comasco et al., 2021).

2.2. Procedures

The daily treatment consisted of a second generation SPRM, ulipristal acetate (UPA) 5 mg (Esmya®) (Wagenfeld et al., 2013) or placebo tablets, on a three-month continuous regimen initiated on the first day of menses (Comasco et al., 2021).

2.3. Hormone analyses

Levels of oestradiol, progesterone, testosterone, and cortisol, were assessed using venous blood samples, taken at the beginning of each scanning session. Steroid hormones were measured in serum at the Core Facility of Metabolomics at the University of Bergen by liquid chromatography - tandem mass spectrometry (supplementary material).

2.4. MR acquisition

Brain scanning sessions were performed in two instances; once at baseline, in the late luteal phase (day 0 - (−7)) before treatment, and once at follow-up, in the end of the last treatment cycle. For women still having a regular menstrual cycle (not affected by the treatment), the follow-up scan coincided with the late luteal phase of the last treatment month. More information can be found in (Comasco et al., 2021).

Scans were acquired on a 3.0 Tesla whole-body scanner (Achieva dStream, Philips Medical Systems, Best, The Netherlands) equipped with a 32-channel head coil. For the anatomical 3D-T1-weighted whole-brain scans, a MPRAGE sequence was used with the following parameters: TR = 8.3 ms, TE = 3.8 ms, flip angle = 8°, 256 x 256 matrix size, 220 slices, slice thickness = 1 mm, acquisition time = 3:50 min. Resulting images have a 0.94 x 0.94 x 1 mm3 voxel size.

2.5. Voxel-based morphometry

The T1-weighted images were preprocessed using the segmentation routine of Statistical Parametric Mapping (SPM12, Welcome Trust...
Table 1  Demographics, remission, symptom severity, and hormonal level descriptive characteristics of the PMDD patients in the placebo and treatment groups at baseline and follow-up, expressed as n (%) or mean ± SD.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Baseline SPRM(n = 18)</th>
<th>Placebo(n = 17)</th>
<th>Follow-up SPRM(n = 18)</th>
<th>Placebo(n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years a</td>
<td>34.7 (5.3)</td>
<td>35.3 (7.2)</td>
<td>35 (5.4)</td>
<td>35.6 (7.4)</td>
</tr>
<tr>
<td>BMI</td>
<td>24.3 (4.8)</td>
<td>23.3 (2.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>University degree</td>
<td>13 (72.2)</td>
<td>13 (76.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No university degree</td>
<td>5 (27.8)</td>
<td>4 (23.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment</td>
<td>17 (94.4)</td>
<td>13 (76.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working part- or full time</td>
<td>1 (5.6)</td>
<td>3 (17.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1 (5.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response**2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>16 (88.8)</td>
<td>10 (58.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 (5.6)</td>
<td>6 (41.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission**2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>9 (50)</td>
<td>3 (17.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial</td>
<td>7 (38.9)</td>
<td>7 (41.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 (5.6)</td>
<td>7 (41.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRSP Symptom Severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total, score**2</td>
<td>58.9 (18.7)</td>
<td>64.6 (17.1)</td>
<td>38.7 (15.3)</td>
<td>57.7 (19.6)</td>
</tr>
<tr>
<td>Change from baseline (%)a</td>
<td>−21.4</td>
<td>−9.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression score a†</td>
<td>8.9 (2.7)</td>
<td>9.2 (3.6)</td>
<td>5.4 (2.4)</td>
<td>7.7 (3.4)</td>
</tr>
<tr>
<td>Change from baseline (%)a</td>
<td>−32.6</td>
<td>−12.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability score a‡</td>
<td>6.6 (2.8)</td>
<td>6.6 (2.6)</td>
<td>4.00 (2.0)</td>
<td>5.5 (2.3)</td>
</tr>
<tr>
<td>Change from baseline (%)a</td>
<td>−23.7</td>
<td>−4.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety score a**2</td>
<td>3.1 (1.5)</td>
<td>3.1 (1.2)</td>
<td>1.9 (1.0)</td>
<td>2.7 (1.1)</td>
</tr>
<tr>
<td>Change from baseline (%)a</td>
<td>−4.1</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affective Lability score a**2</td>
<td>6.5 (2.6)</td>
<td>7.0 (2.4)</td>
<td>3.8 (2.1)</td>
<td>5.9 (2.2)</td>
</tr>
<tr>
<td>Change from baseline (%)a</td>
<td>−17.6</td>
<td>−11.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormones</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progesterone, nmol/L</td>
<td>21.3 (19.9)</td>
<td>24.4 (16.9)</td>
<td>3.3 (7.8)</td>
<td>18 (16.95)</td>
</tr>
<tr>
<td>Oestradiol, pmol/L</td>
<td>410.9 (266.7)</td>
<td>407.6 (279)</td>
<td>366.6 (300.4)</td>
<td>391.3 (236.7)</td>
</tr>
<tr>
<td>Testosterone, nmol/L</td>
<td>0.9 (0.4)</td>
<td>0.8 (0.3)</td>
<td>0.94 (0.29)</td>
<td>0.85 (0.37)</td>
</tr>
<tr>
<td>Cortisol, nmol/L</td>
<td>295.5 (138.3)</td>
<td>333.7 (154.3)</td>
<td>274.9 (100.9)</td>
<td>252 (82)</td>
</tr>
</tbody>
</table>

*significant between group comparison, p ≤ 0.05; **2 significant between group comparison at follow-up, p ≤ 0.05; † significant within group (SPRM) time comparison, p ≤ 0.05; DRSP, Daily Record of Severity of Problems.

a Deviated from normality, Mann-Whitney U test was performed.

Centre for Neuroimaging, University College London, UK) implemented in MATLAB R2019b (The Mathworks Inc., Natick, MA, USA) (see supplementary material for details). ROIs were a priori defined according to the literature on structures reported to be related to PMDD and progesterone (Dubol et al., 2020): ACC, cerebellum (Cb), insula, inferior (IPL) and superior (SPL) parietal lobules, prefrontal cortex (PFC), inferior (ITG), middle (MTG), and superior temporal gyri (STG), based on the Automated Anatomical labeling (AAL) atlas, and subcortical structures including the nucleus accumbens (Nacc), hippocampus, amygdala, and thalamus.

2.6 Subcortical segmentation

To obtain a more accurate anatomical segmentation of the subcortical structures, the FSL-FIRST automatic segmentation pipeline (Patenaude et al., 2011) was used (see supplementary material for details). The mean volumes of right and left Nacc, hippocampus, amygdala, and thalamus were estimated by the FSLstats tool for further statistical analyses on SPSS Statistics for Windows, version 26 (SPSS Inc., Chicago, Ill., USA).

2.7 Surface-based morphometry

The SPM preprocessing and analyses were carried out using the CAT12 toolbox in SPM12 (Dahnke et al., 2013) (see supplementary material for details). Average surface parameters were additionally extracted from ROIs based on the Desikan-Killiany atlas (Gaser and Dahnke, 2016), including the rostral and caudal ACC, insula, parahippocampal gyrus, STG, MTG, and ITG, SPL and IPL, and nine prefrontal regions including superior frontal, rostral and caudal middle frontal gyrus, pars orbitalis, pars triangularis, pars orbitalis, lateral, and medial orbitofrontal.

2.8 Statistical analyses

Exploratory whole-brain VBM and SPM analyses were run on SPM12. A non-parametric mixed effects model was employed to examine the main and interaction effect of treatment group (SPRM and placebo) and time (before and end of treatment) on GMV and surface measures (cortical thickness, gyrification, sulcal depth and
fractal dimension), using the threshold-free cluster enhancement (TFCE) methodology (Smith and Nichols, 2009) (http://dbm.neuro.uni-jena.de/tfce/) and correction for multiple comparisons across voxels with the family-wise error correction using a threshold of \( p_{FWE} < 0.5 \). Comparisons between the treatment groups at baseline were additionally performed to exclude any bias due to random pre-existing structural differences between the treatment groups. For the ROI analyses, a GLM repeated-measures ANOVA was specified with time (baseline, follow-up) as the within-subjects factor and treatment group (SPRM, placebo) as the between-subjects factor to assess treatment effect based on type III sum of squares on each of the ROI and for each measure (GMV, surface measures), using SPSS version 26. The False Discovery Rate (FDR) correction was applied to correct for the number of significant results, using a lenient threshold of \( q < 0.1 \), due to the exploratory nature of the analysis. Bayesian repeated measures ANOVAs were performed on JASP (Version 0.16) to determine the strength of the interaction. Additionally, we assessed the treatment effect on GMV in a voxel-wise manner in the dorsal ACC/dorsomedial PFC (dACC/dmPFC) cluster, where differential reactivity to the aggressive response condition was found between treatment groups in our functional neuroimaging study on a similar sample (Katsouni et al., 2021). For this analysis, the TFCE approach was applied, with a FWE correction for multiple testing at the \( p < 0.05 \) threshold.

Furthermore, putative effects of change in symptom severity over time and treatment group on brain structure were evaluated by means of linear regression. Mean GMV was extracted from the a priori defined ROIs and change (\( \Delta \)) in GMV was computed by subtracting the follow-up mean GMV from the baseline mean GMV. Similarly, the \( \Delta \) for the surface metrics was computed. Linear regression models were run using the change (\( \Delta \)) in regional mean GMV, cortical thickness, gyration index, sulcal depth, and fractal dimension as outcome variables, the change in the four core symptom severity (\( \Delta \)DRSP depression, \( \Delta \)DRSP irritability, \( \Delta \)DRSP anxiety, and \( \Delta \)DRSP affective liability) and treatment group as explanatory variables. Age, body mass index (BMI), and total intracranial volume (TIV) were considered as nuisance covariates in the models. The FDR correction was applied to account for the number of explanatory variables, using the lenient threshold of \( q < 0.1 \). Additional Bayesian linear regression analyses were modelled in the same manner to examine the strength of the evidence.

3. Results

3.1. Descriptives

In total, 35 (SPRM: \( n = 18 \); Placebo: \( n = 17 \)) women were included in the analyses. The two groups did not differ in terms of age, BMI, or TIV (Table 1). At baseline, we found no differences in total DRSP or subscales between treatment groups. At the end of treatment, women with PMDD who had been randomised to SPRM treatment displayed significantly lower total DRSP scores, and lower DRSP anxiety and affective liability scores compared to those receiving placebo (Table 1). Total or partial remission was achieved by 89% of the women receiving SPRM treatment, compared to 59% in the placebo group, with both remission status and response status being significantly different between treatment groups (response: \( p = 0.039 \); remission: \( p = 0.029 \), Table 1).

3.2. Treatment effect on grey matter structure

Baseline grey matter volume did not differ between treatment groups. On the whole-brain level, SPRM treatment was not associated with any change in GMV (Fig. 1) or surface metrics, cortical thickness, gyration index, sulcal depth, and fractal dimension, compared to placebo (Fig. 2). Similarly, we found no main effects of time or treatment group, supplementary material (Table S1).

No significant treatment effects were detected in any of the selected ROIs after correction for multiple testing. Similarly, no treatment effects were noted on subcortical GMV among the four structures (Nacc, hippocampus, amygdala, and thalamus) subjected to subcortical volumetric analyses (Fig. 1). Of note, the slightly more pronounced difference between groups in GMV of the left MFG illustrated in Fig. 1 is not noteworthy, as it corresponds to around \( 0.01 \cdot 0.5 \) mm\(^3\). Additionally, no significant treatment effect was observed on the surface metrics of any selected ROIs (Fig. 2). Bayesian interaction models reflected no likelihood that the present data can provide evidence for treatment effects on grey matter, as indicated by the Bayes Factor (\( BF_{10} \)) < 1 for all ROIs.

Moreover, the treatment effect on grey matter within the ROI mask built from the functional (dACC/dmPFC) cluster differentially activated in PMDD women during aggressive

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**Table 1** Change (\( \Delta \)) in GMV over time in the SPRM and placebo groups in cortical and subcortical regions. Mean GMV (mm\(^3\)) was extracted from a priori defined anatomical ROIs. Two outliers in the placebo group drive the difference visible in the left MFG; the effect disappears when outliers are removed. ACC, anterior cingulate cortex; AMYG, amygdala; CB crus, cerebral crus; CB lob, cerebellar lobules; CB vermis, cerebellar vermis; HIP, hippocampus; IFG, inferior frontal gyrus; INS, insula; IPL, inferior parietal lobe; ITG, inferior temporal gyrus; L, left; MFG, middle frontal gyrus; MTG, middle temporal gyrus; Nacc, nucleus accumbens; OFC, orbitofrontal cortex; R, right; SFG, superior frontal gyrus; SPL, superior parietal lobe; STG, superior temporal gyrus; THA, thalamus.

**Fig. 1** Change (\( \Delta \)) in GMV over time in the SPRM and placebo groups in cortical and subcortical regions. Mean GMV (mm\(^3\)) was extracted from a priori defined anatomical ROIs. Two outliers in the placebo group drive the difference visible in the left MFG; the effect disappears when outliers are removed. ACC, anterior cingulate cortex; AMYG, amygdala; CB crus, cerebral crus; CB lob, cerebellar lobules; CB vermis, cerebellar vermis; HIP, hippocampus; IFG, inferior frontal gyrus; INS, insula; IPL, inferior parietal lobe; ITG, inferior temporal gyrus; L, left; MFG, middle frontal gyrus; MTG, middle temporal gyrus; Nacc, nucleus accumbens; OFC, orbitofrontal cortex; R, right; SFG, superior frontal gyrus; SPL, superior parietal lobe; STG, superior temporal gyrus; THA, thalamus.
response to provocation (Kaltsouni et al., 2021) was investigated. We found no structural effects of treatment in this ROI mask.

3.3. Effects of symptom severity change, group, and covariates on changes in grey matter structure

Potential relationships between change in regional GMV, cortical thickness, gyrification index, sulcal depth, and fractal dimension and change in the severity of the core symptoms, along with treatment group were assessed, while adjusting for age, BMI, and TIV. Multiple linear regression models confirmed the lack of treatment-dependant effects on brain structure, as treatment group was not a significant predictor in any model for any of the regions. The few significant effects of change in symptom severity on surface metrics accounted only for a small fraction of the variance in surface metrics and did not remain significant after correction for multiple testing. Follow-up Bayesian linear regression analyses indicated no evidence supporting the alternative hypothesis.
4. Discussion

Grey matter structural correlates of SPRM treatment were investigated in women with PMDD. Continuous three-month, low dose, SPRM treatment, while improving symptom severity (Comasco et al., 2021) and enhancing fronto-cingulate activity (Kaltsouni et al., 2021), did not have an impact on GMV and cortical surface. Changes in grey matter structure were not related to changes in symptom severity as an effect of treatment.

The present findings suggest excluding short-term effects on grey matter structure as a biological mechanism underlying the three-month SPRM treatment administration, despite its effects on brain function (Kaltsouni et al., 2021). Instead, the observed functional effects (Kaltsouni et al., 2021) could be due to changes in synaptic transmission or metabolism processes. Indeed, allopregnanolone, the neuroactive metabolite of progesterone, is a putative trigger of PMDD and exerts its action through the GABAergic system (Sundstrom-Poromaa et al., 2020). Nevertheless, the present findings call for future studies on the long-term effects of SPRM treatment on grey matter structure as the question remains if longer regimens are required for any effects to be traceable.

Treatment-wise, the improvement in mood symptom after receiving SPRM treatment for three months shown by the proof-of-concept trial (Comasco et al., 2021) was also visible in the current subsample, as 16 out of 18 people treated with SPRM were found to be responders, which largely allowed to also assess treatment effects on grey matter. Corroborating these results, beneficial effects on premenstrual symptoms have been observed in individuals with premenstrual syndrome, when receiving SPRM treatment on the same dosage and timing regimen for treating uterine leiomyomomas (Chen et al., 2017). However, structural neuroimaging studies on PMDD symptoms relief are virtually missing. Unfortunately, even though different types of treatments such as selective serotoninergic reuptake inhibitors and gonadotropin-releasing hormone agonists have shown efficacy on PMDD symptoms (Hantsoo and Riddle, 2021), their effect on the brain of women with PMDD is not known.

Regarding treatment-dependent relationships between measures of cortical architecture or grey matter volume and symptom change, the current findings do not support any association. Independently of treatment, some symptom change explained a small part of the variance in surface metrics, although these results did not survive correction for multiple comparisons (data not shown), accompanied by Bayesian results not supporting the alternative hypothesis. Taken together, the regression analyses conveyed on the absence of noteworthy effects of SPRM treatment on brain structure.

The present findings should be interpreted in light of some methodological considerations. According to a priori required sample analysis, the present sample was adequate to assess effects of medium size ($\eta^2 = 0.06$) with a power of 0.80 and an alpha coefficient of 0.05 (Paul et al., 2007). Notably, data collection on hormone-related mood disorders can be challenging due to the additional requirements for reliable prospective diagnostic procedures and validity in both psychometric and biological sampling methods (Eisenlohr-Moul, 2019), which can limit the sample size. Regarding treatment effects, a number of studies support the involvement of the progesterone metabolites, such as allopregnanolone, rather than just progesterone to be crucial in the psychopathology of PMDD (Bixo et al., 2017; Hantsoo and Epperson, 2020; Sundstrom-Poromaa et al., 2020). Data on allopregnanolone was not available but would not be expected to be associated with differential grey matter structure as it is the absence of fluctuations of neurosteroids rather than the level per se that is posited to abolish PMDD symptomatology.

The strengths of this study include prospective ratings of symptom severity, multimodal structural analyses, and non-parametric statistical analyses. Additionally, VBM data was used in conjunction with volumetric subcortical analyses, minimizing the risk of false negatives due to the low sensitivity of the VBM registration algorithm in accounting for inter-individual variability (Oakes et al., 2007). Thus, the current design and data analyses offer high sensitivity in tracking anatomical differences between the two groups over time. However, based on the Bayesian analyses, the strength of the present evidence in favour of treatment effect on grey matter is non-existent. Measuring the Bayes Factor offers an advantage over reporting plain significance, as it provides a means of quantifying the data sensitivity in confirming or disproving the null hypothesis (Beard et al., 2016; Kass and Raftery, 1995).

Given the novelty and the exploratory nature of the study, the present findings cannot be conclusive on the absence of an SPRM effect on brain architecture. Sparse and inconsistent findings on the anatomical signatures of PMDD are documented and the methodological differences are noteworthy (Dubol et al., 2020); however, recent findings do not seem to confirm differential grey matter structure in PMDD (Dubol et al., 2022a). These women suffer from this disorder for decades throughout their reproductive years (Rapkin and Winer, 2009) and since luteal-phase structural signatures of the disorder are still to be established, it is likely that three months might not be enough to observe effects on grey matter. In addition, the current sub-sample is smaller than the one included in the clinical trial on which this study is based, thus making it impossible to compare remitters vs. non-remitters in terms of brain correlates of symptom relief (Comasco et al., 2021).

In conclusion, this is the first study investigating the structural correlates of SPRM as treatment for PMDD. The lack of treatment effect on brain structure could either indicate that grey matter changes are not part of the mechanism through which SPRM exerts its action on the brain or that longer administration regimens are required to observe structural alterations. Hormone-based treatments for PMDD have been considered as an alternative due to the efficacy of combined oral contraceptives (COC) or gonadotropin-releasing hormone agonists and antagonists (Hantsoo and Epperson, 2015). Importantly, besides improving mood symptoms, SPRM treatment does not entail neither the severe mental side effects risk as COC have been shown to be associated with (Lundin et al., 2017; Rapkin et al., 2019) nor the hypoestrogenic effects that are linked to gonadotropin-releasing hormone agonists (Mezrow et al., 1994), thus rendering SPRM treatment suitable for long-term regimens.
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Conflict of Interest

RL received travel grants and/or conference speaker honoraria within the last three years from Bruker BioSpin MR, Heel, and support from Siemens Healthcare regarding clinical research using PET/MR. He is a shareholder of the startup company BM Health GmbH since 2019. ISP has served occasionally on advisory boards or acted as invited speaker at scientific meetings for Asarina Pharma, Bayer Health Care, Gideon Richter, Peptonics, Shire/Takeda, Sandoz, and Lundbeck A/S. All other authors declare that they have no conflict of interest.

CRediT authorship contribution statement

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Supplementary materials

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