



Research paper

Cortical morphology variations during the menstrual cycle in individuals with and without premenstrual dysphoric disorder

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ABSTRACT

Background: Premenstrual dysphoric disorder (PMDD) is hypothesized to stem from maladaptive neural sensitivity to ovarian steroid hormone fluctuations. Recently, we found thinner cortices in individuals with PMDD, compared to healthy controls, during the symptomatic phase. Here, we aimed at investigating whether such differences illustrate state-like characteristics specific to the symptomatic phase, or trait-like features defining PMDD.

Methods: Patients and controls were scanned using structural magnetic resonance imaging during the mid-follicular and late-luteal phase of the menstrual cycle. Group-by-phase interaction effects on cortical architecture metrics (cortical thickness, gyrification index, cortical complexity, and sulcal depth) were assessed using surface-based morphometry.

Results: Independently of menstrual cycle phase, a main effect of diagnostic group on surface metrics was found, primarily illustrating thinner cortices ($0.3 < \text{Cohen's } d > 1.1$) and lower gyrification indices ($0.4 < \text{Cohen's } d > 1.0$) in patients compared to controls. Furthermore, menstrual cycle-specific effects were detected across all participants, depicting a decrease in cortical thickness ($0.4 < \text{Cohen's } d > 1.7$) and region-dependent changes in cortical folding metrics ($0.4 < \text{Cohen's } d > 2.2$) from the mid-follicular to the late luteal phase.

Limitations: Small effects ($d = 0.3$) require a larger sample size to be accurately characterized.

Conclusions: These findings provide initial evidence of trait-like cortical characteristics of the brain of individuals with premenstrual dysphoric disorder, together with indications of menstrual cycle-related variations in cortical architecture in patients and controls. Further investigations exploring whether these differences constitute stable vulnerability markers or develop over the years may help understand PMDD etiology.

1. Introduction

Fluctuations in ovarian hormones over the life of individuals that menstruate have been repeatedly proven to shape the brain, both in the short term (i.e. across the menstrual cycle) and over longer time periods (e.g. puberty and pregnancy) (Carmona et al., 2019; Dubol et al., 2021; Rehbein et al., 2021). Of relevance to mental health, accumulating evidence shows that these periods of endocrine shifts are associated with a higher prevalence of mood and anxiety disorders (Hodes and Epperson, 2019; Soares and Zitek, 2008). The co-occurrence of these hormonal variations and psychiatric symptoms represents a remarkable

opportunity to explore the interaction of various biological factors (e.g. hormones, brain features) and their impact on mental health.

The long understudied premenstrual dysphoric disorder (PMDD) perfectly illustrates this concept, as a hormone-related chronic condition affecting individuals in childbearing age, which has been only quite recently recognized as a depressive disorder in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (A.P.A., 2013). This disorder, specific to menstruating individuals' mental health, is characterized by cyclical affective symptoms (depressed mood or hopelessness or self-deprecation, anxiety or tension, irritability or anger or increased interpersonal conflict, and lability of affect) that peak in the

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luteal phase of the menstrual cycle, and subside shortly after the onset of the next menses. Despite its prevalence and psychosocial burden (Reilly et al., 2024; Wikman et al., 2022), very little is known about the neurobiology of PMDD (Comasco and Sundstrom-Poromaa, 2015). The onset of symptoms is conditional on the variations in estradiol and progesterone levels during the menstrual cycle (Schmidt et al., 2017), while maintaining low and stable levels of these hormones lead to symptom improvement (Comasco et al., 2021; Wyatt et al., 2004). Nevertheless, no difference in ovarian hormones levels was ever clearly established between individuals with PMDD and healthy controls (Epperson et al., 2012).

The affective nature of PMDD core symptoms points to an impaired corticolimbic processing, involving an altered top-down inhibitory control over limbic brain structures (Dubol et al., 2020). Yet, as a relatively new field of research, neuroimaging studies of PMDD neural underpinnings are scarce. Mostly focused on investigating functional variations in patients with PMDD across the menstrual cycle, only three studies had explored morphological alterations in the PMDD brain (Berman et al., 2013; Jeong et al., 2012; Syan et al., 2017). Recently, we found evidence of thinner cortices throughout the brain in patients compared to controls during the luteal phase, without any alteration of cortical folding (Dubol et al., 2022a). While this was the first work to explore differences in cortical folding metrics in PMDD, a prior study had investigated cortical thickness differences between a smaller sample of patients and controls, yet focusing primarily on PMDD and bipolar disorder comorbidity without accounting for interpersonal variations in total intracranial volume (Syan et al., 2017). Furthermore, the interaction effect of PMDD diagnosis and menstrual cycle phase on cortical architecture remains so far uninvestigated. Hence, it is still unclear whether differential cortical thickness or folding characterize the brain of patients and if they represent trait-like features specific to the disorder, or state-like properties that are dependent on the menstrual cycle phase.

Prior indication of diagnosis-specific cortical architecture traits comes from structural MRI studies investigating anxiety, mood, and personality disorders, whose symptoms partly overlap with those of PMDD, showing thinner cortices (Hibar et al., 2018; Molent et al., 2018; Schmaal et al., 2017), and reduced cortical folding in patients compared to controls (Chen et al., 2021; Depping et al., 2018). It is thus possible that deviations in cortical architecture, occurring throughout brain development, might predispose or increase the vulnerability to PMDD. On the other hand, increasing evidence of hormones-related brain structural plasticity across the menstrual cycle (Dubol et al., 2021) suggests that menstrual cycle phase-specific alterations in cortical grey matter structure could potentially occur in patients with PMDD. At the cortical level, healthy, regularly cycling individuals display thicker cortices in orbitofrontal and inferior parietal areas when ovarian hormones levels are low, compared to the rest of the menstrual cycle (Meeker et al., 2020; Petersen et al., 2014). However, menstrual cycle-related variations in cortical folding remain unexplored.

Here we aimed at investigating cortical architecture in individuals with PMDD and healthy controls across the menstrual cycle, to determine if ovarian hormones-related variations of brain surface morphology occur in healthy, regularly cycling individuals, and to highlight potential state- versus trait-like alterations in grey matter surface metrics in patients. We expected to find variations in cortical architecture metrics across the menstrual cycle, based on prior work providing evidence of short-term, plastic changes in cortical thickness (Meeker et al., 2020; Petersen et al., 2014). In patients compared to controls, we hypothesized that the recently reported differences in cortical thickness (Dubol et al., 2022a) represent trait-like characteristics that are stable across the menstrual cycle, based on recent observations of trait-like differences in grey matter volumes (Stiernman, Dubol et al., under review).

2. Methods

2.1. Participants

The study was conducted at the Umeå University Centre for Functional Brain Imaging, Sweden. In total, we recruited thirty-two individuals with PMDD and thirty-two healthy controls, by means of advertisement in local newspapers, a student website for clinical trials, social media platforms, and information boards at out-patient clinics and on the Umeå University campus. Participants were included if they met the following criteria: age 18–45 years, regular menstrual cycles (25–31 days), non-hormonal contraception. Participants allocated to the PMDD groups had to fulfill PMDD diagnostic criteria according to the DSM-5. Exclusion criteria for both patients and healthy controls were: current use of steroid hormones and/or psychotropic medication, significant somatic conditions, drug or alcohol misuse, pregnancy and contraindications to MRI. For previous use of psychotropic and steroid hormones (including hormonal contraception) drugs, we required wash-out periods of three and one months prior to inclusion, respectively. All participants were assessed using the Mini International Neuropsychiatric Interview (MINI) questionnaire to exclude any psychiatric comorbidity. Previous major depressive episodes were allowed, on the condition that the participant was in remission for more than two years prior to the study. The participants prospectively completed daily ratings of PMDD symptom severity for a minimum of two menstrual cycles using the Daily Record of Severity of Problems (DRSP) (Endicott et al., 2006), implemented via an ad-hoc web platform. The study was approved by the Regional Ethical Review Board in Umeå (2016-111-31M, 2017-266-32M), and all participants provided written informed consent to participate in the study. The study conforms to the provisions of the Declaration of Helsinki.

PMDD diagnosis, as defined by DSM-5, was confirmed using the prospective DRSP scores with the following criteria: mild average daily symptom severity (score ≤ 3) during the mid-follicular phase (days +6 to +10 after the onset of menses), moderate symptom severity (score ≥ 4) on at least two days during the late-luteal phase (days –5 to –1 prior to the onset of menses), including minimum one “core” mood symptom and at least five symptoms in total. The “core” mood symptoms include depressed mood or hopelessness or self-deprecation, anxiety or tension, irritability or anger or increased interpersonal conflict, and lability of affect. Symptoms in the late-luteal phase also had to, at least moderately, interfere with daily functioning (score ≥ 4 for two days on at least one impairment item). If the above criteria were met for two consecutive menstrual cycles, and if the assessment of the daily ratings were in agreement with the clinical judgement of the investigator, a PMDD diagnosis was given. For participants included in the control group, low symptoms ratings were required across the entire menstrual cycle (score < 3).

2.2. Study design

Each participant took part in two scanning sessions, once in the mid-follicular phase (day +5 to +11), and once in the late-luteal phase (day –7 to –1) (Fig. 1). The order of the two scanning sessions was counter-balanced across participants within each group so that half started with the mid-follicular assessment and half started with the late luteal assessment. Blood samples were collected during each scanning session. The assessment windows were confirmed using self-reported previous and next menses, as well as serum concentrations of estradiol and progesterone. Progesterone and estradiol serum concentrations were analyzed separately using Elecsys® Gen III immunoassays by the central hospital laboratory at Norrlands University Hospital, Umeå, Sweden. In order to ensure that none of the participant was assessed during an anovulatory cycle, serum progesterone levels were compared to day-to-day progesterone concentrations during an idealized menstrual cycle (Sundstrom-Poromaa et al., 2020), allowing up to two standard

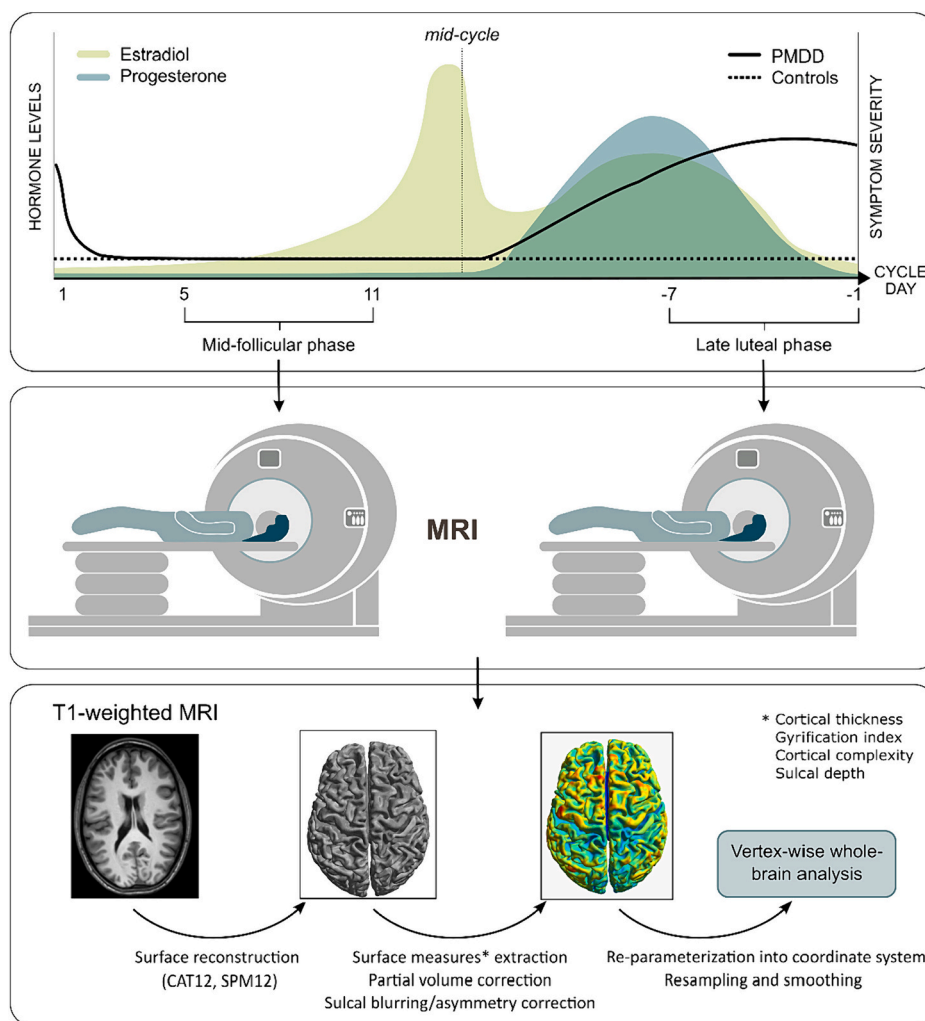


Fig. 1. Study design. Patients with PMDD and healthy controls were assessed twice; once in the asymptomatic, mid-follicular phase (day 5 to day 11 after the previous menses) and once during the symptomatic, late luteal phase (day –7 to –1 before the next menses) of the menstrual cycle. Structural MRI brain data was collected on both occasions, to measure grey matter morphology throughout the cycle. The brain images were preprocessed using the CAT12 toolbox in SPM12. Vertex-wise exploratory analyses of the surface measure maps were conducted in SPM12 to detect group-by-phase interaction effects on cortical thickness, gyrfication index, cortical complexity (fractal dimension) and sulcal depth throughout the brain. The main effects of group (PMDD versus Controls) and phase (mid-follicular versus late luteal) were also assessed. MRI, Magnetic Resonance Imaging; PMDD, PreMenstrual Dysphoric Disorder.

deviations from the standard curve.

2.3. MR acquisition

High-resolution T1-weighted images were acquired on a 3.0 Tesla Discovery MR750 scanner (General Electric, Madison, WI, USA) equipped with a 32-channel head coil, using a 3D fast spoiled gradient echo sequence with the following parameters: TR = 8.2 ms, TE = 3.2 ms, 512×512 matrix size, flip angle = 12° , 176 transversal slices, acquisition time = 8:11 min. Resulting images have a $0.48 \times 0.48 \times 1 \text{ mm}^3$ voxel size.

2.4. Surface-based morphometry

The pre-processing and analyses of T1-weighted images were run using the Statistical Parametric Mapping software (SPM12, Wellcome Trust Centre for Neuroimaging, University College London, UK) and the CAT12 toolbox (<http://dbm.neuro.uni-jena.de/cat>), implemented in MATLAB R2019b (MathWorks, Natick, MA, USA). The CAT12 surface-based morphometry (SBM) pre-processing pipeline (Fig. 1) includes a projection-based thickness estimation (Dahnke et al., 2013), along with

partial volume correction and correction for sulcal blurring and sulcal asymmetries. In addition, a gyrfication index was extracted based on absolute mean curvature (Luders et al., 2006), and cortical complexity and sulcal depth measures were extracted. The surface meshes were re-parameterized into a common coordinate system using spherical maps (Yotter et al., 2011b), allowing for inter-subject comparisons. All surface measures were resampled and smoothed with a Gaussian kernel, of 15 mm (FWHM) for cortical thickness and 20 mm (FWHM) for the other parameters, based on the recommended settings. The automated CAT12 quality control module for surface data was used to detect outliers.

Part of the present SBM data (luteal phase data) has been used in a recent publication focusing on differences between patients and healthy controls during the symptomatic phase of the menstrual cycle (Dubol et al., 2022a). The research question here investigated – whether cortical architecture alterations in PMDD vary across the menstrual cycle – differs from the hypothesis tested in our previous publication.

2.5. Statistical analyses

First, group-by-phase interaction effects on surface metrics (cortical thickness, gyrfication index, cortical complexity, and sulcal depth) were

assessed using a whole-brain vertex-wise exploratory analysis in SPM12, based on the general linear model using a flexible factorial design (repeated-measures analysis of variance). The variable ‘Group’ (PMDD, controls) was defined as between-subject factor, and the variables ‘Phase’ (mid-follicular, late-luteal) and ‘Subject’ were set as within-subject factors. Statistical significance was set at $p < 0.1$, using Family-Wise Error (FWE) correction and Threshold-Free Cluster Enhancement (TFCE).

Second, the main effects of Group (across phases) and Phase (across groups) were assessed using two-samples *t*-test and paired-*t*-test designs, respectively. As for the main analysis, statistical significance was set at $p < 0.1$, FWE-corrected using TFCE.

3. Results

3.1. Participants' characteristics

The participants' demographic and endocrine characteristics are presented in the supplementary table 1. Individuals with PMDD did not differ from healthy controls in terms of age, body mass index, total intracranial volume, parity, menstrual cycle length, or prior psychiatric problems. The menstrual cycle timing at scanning, as well as estradiol and progesterone concentrations did not differ between the groups.

3.2. Surface-based morphometry findings

Across brain surface metrics, no significant group-by-phase interaction effect was found within the whole cortex ($p_{FWE} < 0.1$), suggesting that PMDD diagnosis does not interfere with the effect of menstrual cycle phase on cortical morphology, and conversely, that the menstrual cycle does not influence the effect of PMDD diagnosis on cortical morphology. The main effects of group and menstrual cycle phase on cortical thickness, gyrification index, cortical complexity, and sulcal depth were thus explored across menstrual cycle phases, and within the whole sample of participants, respectively.

• Thinner cortices in PMDD

In line with our hypothesis of trait-like brain surface markers of PMDD, we detected thinner cortices in patients compared to controls, independently of menstrual cycle phase ($0.3 < \text{Cohen's } d > 1.1$) (Fig. S1). This main diagnostic group effect on cortical thickness was mostly found in the left hemisphere, within the superior and middle temporal gyri, anterior insula, inferior parietal lobule and fusiform gyrus ($p_{FWE} < 0.05$, Fig. 2, supplementary table 2). In addition, thinner cortices were found in a cluster covering the right superior temporal gyrus and insula in patients compared to controls, although at a less

significant level ($p_{FWE} < 0.1$, supplementary table 2).

• Menstrual cycle-related variations in cortical thickness

Across all participants, thinner cortices in regions of the right hemisphere characterized the late luteal phase compared to the mid-follicular phase ($0.4 < \text{Cohen's } d > 1.7$) (Fig. S2), particularly in the inferior parietal lobule, the posterior part of the superior temporal gyrus and the orbital inferior frontal gyrus ($p_{FWE} < 0.05$, Fig. 2, supplementary table 3). No significant increase in cortical thickness was found across the menstrual cycle.

• Altered cortical folding in PMDD

A main effect of group on folding metrics was observed, showing a smaller gyrification index in patients compared to controls across the menstrual cycle ($0.4 < \text{Cohen's } d > 1.0$) (Fig. S1), in a few clusters covering parts of the left occipital lobe (middle and superior occipital gyri), the left inferior postcentral gyrus, and the bilateral paracentral area ($p_{FWE} < 0.05$, Fig. 3, supplementary table 2). Furthermore, a lower cortical complexity of the right cuneus was detected in patients compared to controls ($p_{FWE} < 0.05$, $0.4 < \text{Cohen's } d > 0.8$, Fig. 3, supplementary table 2). Of note, no significant main effect of group on sulcal depth was detected.

• Menstrual cycle phase-related variations in cortical folding

Menstrual cycle phase-related variations were detected for all three cortical folding measures, illustrating bidirectional changes between phases as described below (Fig. S2).

Deeper sulci were found in the late luteal phase across patients and controls exclusively in regions of the right hemisphere, primarily within the posterior middle temporal gyrus and inferior parietal lobule, but also in the anterior insula/medial orbitofrontal area (TFCE $p_{FWE} < 0.05$, $0.6 < \text{Cohen's } d > 1.7$, Fig. 4, supplementary table 3).

In addition, the gyrification index showed diverging patterns of variations across the menstrual cycle. An increased index was found in the late luteal phase ($p_{FWE} < 0.05$, $0.6 < \text{Cohen's } d > 1.8$, Fig. 4, supplementary table 3), particularly located in the right pre- and post-central areas, the right anterior insula, and the left inferior parietal lobule (inferior part of the supramarginal gyrus). Yet, a decreased index in the right inferior parietal lobule (angular gyrus), the left inferior parietal lobule (superior part of the supramarginal gyrus), as well as the left anterior insula and left pre- and postcentral areas also characterized the late luteal phase ($p_{FWE} < 0.05$, $0.4 < \text{Cohen's } d > 2.2$, Fig. 4, supplementary table 3).

Similarly, measures of cortical complexity displayed both positive

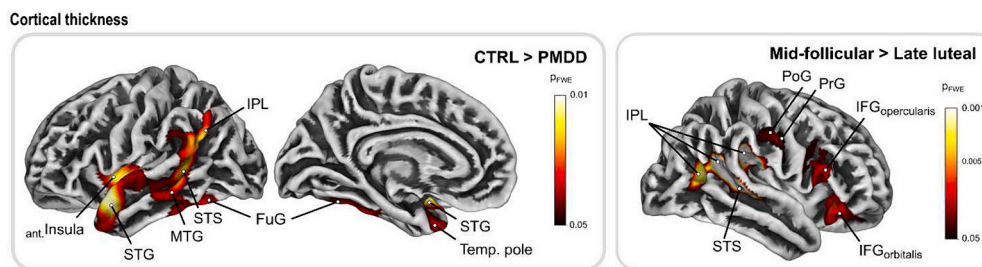


Fig. 2. PMDD diagnosis and menstrual cycle effects on cortical thickness ($p_{FWE} < 0.05$, TFCE). Surface representation of the significant clusters showing: thinner cortex in individuals with PMDD compared to healthy controls across the whole brain throughout the follicular and luteal phases (left panel), and cortical thinning from the mid-follicular to the late luteal phase across the whole brain, among individuals with PMDD and healthy controls (right panel). No significant main effects of Group and Phase were found in the opposite directions. Abbreviations: antInsula = anterior insula, CTRL = healthy controls, FuG = fusiform gyrus, FWE = Family Wise Error correction, IFG = inferior frontal gyrus, IPL = inferior parietal lobule, MTG = middle temporal gyrus, PMDD = premenstrual dysphoric disorder, PoG = postcentral gyrus, PrG = precentral gyrus, STG = superior temporal gyrus, STS = superior temporal sulcus, Temp. pole = temporal pole, TFCE = Threshold Free Cluster Enhancement.

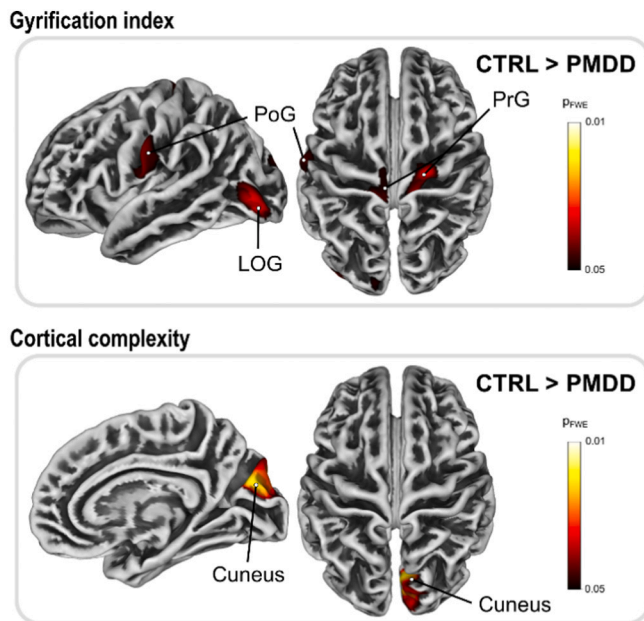


Fig. 3. PMDD diagnosis effect on cortical folding metrics ($p_{FWE} < 0.05$, TFCE). Surface representation of the significant clusters showing: smaller gyrification index (upper panel) and lower cortical complexity (lower panel) in individuals with PMDD compared to healthy controls across the whole brain throughout the follicular and luteal phases. No significant main effects of Group were found on sulcal depth measures. Abbreviations: CTRL = healthy controls, FWE = Family Wise Error correction, LOG = lateral occipital gyrus, PMDD = premenstrual dysphoric disorder, PoG = postcentral gyrus, PrG = precentral gyrus, TFCE = Threshold Free Cluster Enhancement.

and negative changes across menstrual cycle phases. Cortical complexity increased from the mid-follicular phase to the late luteal phase ($0.4 < \text{Cohen's } d > 1.6$), primarily within a cluster including the anterior part of the left superior- and middle temporal gyri, the left anterior insula, and the left orbitofrontal area, as well as in the right inferior parietal lobule (supramarginal gyrus), pre- and postcentral gyri and middle frontal gyrus ($p_{FWE} < 0.05$, Fig. 4, supplementary table 3). Conversely, cortical complexity decreased during the menstrual cycle ($0.4 < \text{Cohen's } d > 1.9$), primarily in the inferior postcentral and parietal gyri, inferior parietal lobule (angular gyrus), Heschl gyrus and precentral gyrus in the left hemisphere, and the anterior insula/orbitofrontal area, dorsal insula, inferior precentral gyrus, superior temporal pole and dorsal postcentral gyrus in the right hemisphere ($p_{FWE} < 0.05$, Fig. 4, supplementary table 3).

4. Discussion

The present study investigated variations in cortical architecture during the menstrual cycle in individuals with PMDD and controls. To this end, participants were scanned twice using structural MRI, once in the mid-follicular phase and once in the late luteal phase, which are characterized in patients by the remission and the peak in symptoms severity, respectively. Differences in surface metrics variations from the mid-follicular to the late luteal phase based on diagnostic groups were assessed using group-by-phase interaction analyses, which yielded negative results, thus excluding state-dependent PMDD-specific cortical surface alterations.

It is noteworthy that we detected a main effect of diagnostic group (PMDD versus controls) across menstrual cycle phases, and a main effect of phase (mid-follicular versus late luteal) across groups on brain surface measures, indicating trait-like surface characteristics of PMDD, and menstrual cycle-specific variations in cortical architecture. The most significant findings ($p_{FWE} < 0.05$, TFCE) show large group effects,

illustrated by thinner cortices (Cohen's d up to 1.1) and smaller gyrification indices (Cohen's d up to 1.0) in patients compared to controls. Likewise, large effects of menstrual cycle phase on cortical thickness (Cohen's d up to 1.7), gyrification index (Cohen's d up to 2.2), sulcal depth (Cohen's d up to 1.7) and cortical complexity (Cohen's d up to 1.9) were detected, depicting a decrease in cortical thickness and region-dependent changes in cortical folding metrics from the mid-follicular to the late luteal phase in both individuals with and without PMDD.

4.1. PMDD-specific cortical morphology

The present findings of thinner cortices in patients compared to controls across menstrual cycle phases corroborate our prior findings indicating lower cortical thickness in PMDD in the symptomatic phase (Dubol et al., 2022a), and additionally indicate trait-like cortical characteristics of the PMDD brain. Notably, thinner cortices were found primarily within the temporal lobe and the inferior parietal cortex, which are both hypothesized to play a role in the pathophysiology of PMDD (Long et al., 2022; Meeker et al., 2020). Trait-like differences in cortical thickness are also in line with our report of trait-like alterations of grey matter volumes in PMDD, including regions where cortical thinning was here associated with the disorder (Dubol, Stiernman, under review). Our findings however contrast with those of a previous study, reporting no difference in cortical thickness between patients and healthy controls, as tested in the mid-follicular and the late luteal phase, separately (Syan et al., 2017). With smaller samples and group comparisons being exclusively tested in each phase separately (as opposed to repeated-measures ANOVA testing for main and interactive effects of group and phase), it is likely that the previous negative findings (Syan et al., 2017) are explained by a lack of statistical power. In the present study, lower measures of cortical folding in a few visual and sensorimotor areas were also found to characterize individuals with PMDD compared to healthy controls across menstrual cycle phases, as illustrated by a smaller gyrification index in occipital and paracentral areas and a lesser complexity of the cuneus. This constitutes, to date, the first piece of evidence suggesting trait-like folding characteristics of PMDD. In line with reduced folding metrics in PMDD, we previously reported negative associations between PMDD symptom severity and both gyrification index and cortical complexity measures in individuals with PMDD scanned during the late luteal phase, including occipital and paracentral regions (Dubol et al., 2022b). Whether these trait-like differences in cortical architecture constitute predisposing factors leading to a heightened vulnerability to develop PMDD or represent secondary markers of the disease progression remains to be determined. The rapid efficacy of intermittent use of selective serotonin reuptake inhibitors (SSRIs) in PMDD, together with our results, also raises the question of symptom relief mechanisms. In major depression, SSRI treatment has been associated with an increase in cortical thickness, suggesting a reversing effect on cortical thinning (Koenig et al., 2018; Nemati and Abdallah, 2020). While the gold standard treatment for PMDD (i.e. SSRI) alleviates symptoms within days (Steinberg et al., 2012), and might rely on a distinct mechanism of action, it is currently unknown whether efficacious treatment in PMDD can reverse trait-like differences in cortical architecture.

Large cohorts-based meta-analyses of structural neuroimaging data report similar cortical alterations across multiple psychiatric disorders, notably highlighting thinner cortices in patients with major depressive disorder, bipolar disorder, or schizophrenia, with a potential effect of illness duration (Cheon et al., 2022). Several studies further point to a lesser gyrification in major depressive disorder (Chen et al., 2021; Depping et al., 2018), bipolar disorder (Choi et al., 2022), and generalized anxiety disorder (Zhang et al., 2022), which share some of the PMDD symptoms. Yet scarcer, studies investigating other measures of cortical folding suggest lower cortical complexity in bipolar disorder and schizophrenia (Trevisan et al., 2022; Yotter et al., 2011a), as well as lower sulcation in both unipolar and bipolar depression (Lener et al.,

metrics we observed are in line with previous neuroimaging studies suggesting ovarian hormones-mediated structural neuroplasticity (Catenaccio et al., 2016). Interestingly, our findings on gyrification indices and cortical complexity measures describe lateralized effects, with opposite patterns of variations occurring in the homologous regions of the left and right hemisphere during the menstrual cycle. We additionally found a decrease in cortical thickness from the mid-follicular to the late luteal phase of the menstrual cycle, within the right orbital inferior frontal gyrus of individuals with PMDD and healthy controls. This is in line with a previous study showing thinner lateral orbitofrontal cortices in naturally cycling individuals in their mid-follicular phase compared to those in their luteal phase (Petersen et al., 2015). Our findings extended the prior ones, by further including the right inferior parietal lobule and the posterior superior temporal gyrus. Interestingly, variations in the neuroanatomical plasticity of the inferior parietal lobule throughout the menstrual cycle have been recently brought to light, indicating greater cortical thickness in this region during menses compared to the rest of the cycle (Meeker et al., 2020), consistently with the present findings. While the literature on menstrual cycle-related variations in cortical architecture is limited, these findings altogether point to a region-specific decrease in cortical thickness in the late luteal phase compared to the mid-follicular phase of the menstrual cycle. Furthermore, surface-based morphometry studies on pregnancy (Chechko et al., 2021; Zhang et al., 2020) indicate that variations in cortical thickness and folding can occur concomitantly with shifts in the hormonal milieu, illustrating a framework for structural neuroadaptive variations associated with fluctuations in ovarian hormones levels. Thus, such hormone-related neuroplastic processes might account for the menstrual-cycle effects herein reported.

4.3. Strengths and limitations

Our study displays a number of strengths in the context of the neuroimaging literature on PMDD, such as the use of the DRSP scale (Endicott et al., 2006) for the definition of both the patients and controls, as well as the confirmation of menstrual cycle phase by use of both cycle mapping and hormonal assessment. It is also worth noting that we employed a whole-brain vertex-wise approach, which offers the advantage of conducting exploratory analyses without restrictive a priori hypotheses and assumptions about anatomically defined brain regions that may not be functionally homogeneous. Furthermore, with a sample size of 55 individuals included in the analyses, our findings reached a statistical power up to 0.9 for the main effect of group (Cohen's $d = 1.1$), and 1.0 for the main effect of menstrual cycle (Cohen's $d = 2.2$). However, yet significant at the $p_{FWE} < 0.05$ threshold, our findings include peaks showing smaller effects ($d = 0.3$), which should be considered with caution (Faul et al., 2007), and call for replication in larger samples.

The present findings represent the first evidence of trait-like cortical characteristics of the PMDD brain, notably pointing to thinner temporo-parietal cortices and smaller folding metrics within occipital areas in PMDD. Future investigations should work on elucidating whether these PMDD-specific structural characteristics constitute vulnerability traits, or whether they are gradually established with the disease duration. In addition, the findings provide novel indications of menstrual cycle-related variations in cortical architecture in individuals with and without PMDD, suggesting ovarian hormone-related neuroplastic processes impacting grey matter thickness and shape.

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CRediT authorship contribution statement

Manon Dubol: Formal analysis, Software, Visualization, Writing – original draft. **Louise Stiernman:** Data curation, Investigation, Methodology, Project administration, Resources, Writing – original draft. **Inger Sundström-Poromaa:** Conceptualization, Funding acquisition, Resources, Writing – review & editing. **Marie Bixo:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Erika Comasco:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

ISP has served on advisory boards or acted as invited speaker at scientific meetings for Asarina Pharma, Bayer Health Care, Gedeon Richter, Peptonics, Shire/Takeda, Sandoz, and Lundbeck A/S, on few occasions. These entities were not involved in the design, conduct or report of the present research. No conflicts of interest are declared by the other authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jad.2024.03.130>.

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