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Neuroimaging progesterone receptor modulation in patients with premenstrual dysphoric disorder

Is it just in your head?

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Abstract
Kaltsouni, E. 2024. Neuroimaging progesterone receptor modulation in patients with premenstrual dysphoric disorder. Is it just in your head? *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 2014. 88 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-2026-7.

Premenstrual dysphoric disorder (PMDD) is a menstrually related mood disorder affecting about 5% of women during their reproductive years. The disorder is cyclic, with the symptomatology namely occurring at the luteal phase of a menstrual cycle, for most ovulatory menstrual cycles and entails a series of mood and physical symptoms. A neural susceptibility to regular hormonal fluctuations is hypothesized as the neuropathophysiological mechanism. While treatment options, such as selective serotonin reuptake inhibitors and hormonal interventions, are available, the neural mechanisms underlying symptom relief remain largely unclear. In this series of studies, a multimodal neuroimaging design was approach was used to reveal the neural correlates of three-month, low-dose selective progesterone receptor modulator (SPRM) treatment in comparison to a placebo. This treatment has been demonstrated to be effective in alleviating psychological symptoms associated with PMDD. Thirty-five women with fulfilling the criteria of a PMDD diagnosis were randomized to treatment with SPRM or placebo, with structural and functional MRI scans conducted before and after randomization. Findings indicated enhanced fronto-cingulate activity during a reactive aggression task in the SPRM treatment group compared to placebo, along with a negative association between aggressive responding and brain activity in the placebo group. Resting state functional connectivity was additionally altered after treatment with SPRM in fronto-visual, temporo-insular, and temporo-cerebellar regions. Additionally, a positive correlation was observed between the reduction in cortisol levels and the decrease in temporo-insular connectivity. No treatment effects were observed on brain structure, including grey and white matter volume, as well as cortical surface architecture. Lastly, White matter microstructure integrity did not differ longitudinally but showed cross-sectional differences. In conclusion, the effects of SPRM treatment were primarily observed in brain function, specifically in terms of enhanced cognitive control processing in the context of reactive aggression and resting state functional connectivity in regions relevant to cognitive and sensorimotor processing, with no significant structural alterations noted. Taken together, these findings confirm that the fluctuations rather than absolute levels of ovarian hormones are primary contributing to premenstrual symptomatology, potentially through hormonal-state dependent functional correlates.

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Για τη Λένα, for Fadhila

Κρείττον οψιμαθή είναι ή αμαθή
Better to have learned recently than not at all
~Socrates

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Kaltsouni, E., Fisher, P. M., Dubol, M., Hustad, S., Lanzenberger, R., Frokjaer, V. G., Wikström, J., Comasco, E.*, & Sundström-Poromaa, I.* (2021). Brain reactivity during aggressive response in women with premenstrual dysphoric disorder treated with a selective progesterone receptor modulator. *Neuropsychopharmacology*, 46(8), 1460-1467.

II. Kaltsouni, E., Dubol, M., Wikström, J., Lanzenberger, R., Sundström-Poromaa, I.*, & Comasco, E.* (2022). Grey matter morphology in women with premenstrual dysphoric disorder treated with a selective progesterone receptor modulator. *European Neuropsychopharmacology*, 65, 35-43.

III. Kaltsouni, E., Gu, X., Wikström, J., Hahn, A., Lanzenberger, R., Sundström-Poromaa, I.*, & Comasco, E.* White matter integrity in individuals with premenstrual dysphoric disorder treated with selective progesterone receptor modulator treatment. Manuscript

IV. Kaltsouni, E., Wikström, J., Lanzenberger, R., Sundström-Poromaa, I.*, & Comasco, E*. (2024) White matter volume and treatment with selective progesterone receptor modulator in people with premenstrual dysphoric disorder. *Psychoneuroendocrinology*, 106977.

V. Kaltsouni, E., Wikström, J., Lanzenberger, R., Sundström-Poromaa, I.*, & Comasco, E*. Selective progesterone receptor modulation and brain activity at rest in patients with premenstrual dysphoric disorder. Manuscript

Papers not included in the thesis:

VI. Kaltsouni, E., Schmidt, F., Zsido R. G, Eriksson A., Sacher J, Sundström-Poromaa, I., Sumner, R. L., & Comasco, E. (2024). Rachael L. Electroencephalography Findings in Menstrually-Related Mood Disorders: A Critical Review. *Frontiers in Neuroendocrinology.*

Contents

Abbreviations

ACC	Anterior cingulate cortex
AD	Axial diffusivity
AQ-RSV	Aggression Questionnaire-revised Swedish version
BDNF	Brain derived neurotrophic factor
BOLD	Blood- oxygenation- level- dependent
CbP	Posterior Cerebellum
CI	Confidence interval
CNS	Central nervous system
CSF	Cerebrospinal fluid
dACC	Dorsal anterior cingulate cortex
dmPFC	Dorsomedial prefrontal cortex
DMN	Default mode network
DRSP	Daily report severity of problems
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTI	Diffusion tensor imaging
EMA	European Medicines Agency
EPI	Echo-planar imaging
FA	Fractional anisotropy
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
FWHM	Full width at half maximum
FWE	Family-wise error
GABA	γ-Aminobutyric acid (gamma-aminobutyric acid)
GLM	General linear model
GnRH	Gonadotropin releasing hormone
IC	Insular cortex
LH	Luteinizing hormone
LN	Language network
MADRS	Montgomery-Asberg Depression Rating Scale
MD	Mean diffusivity
MNI	Montreal Neurological Institute
mPFC	Medial prefrontal cortex
MRI	Magnetic resonance imaging

OFC	Orbitofrontal cortex
OLS	Ordinary least squares
PFC	Prefrontal cortex
PMDD	Premenstrual dysphoric disorder
PPI	Psychophysiological interaction
PSAP	Point subtraction aggression paradigm
pSTG	Posterior superior temporal gyrus
RD	Radial diffusivity
ROI	Region of interest
rs-FC	Resting state functional connectivity
SBC	Seed-base connectivity
SBM	Surface-based morphometry
SFG	Superior frontal gyrus
SNR	Signal-to-noise ratio
SPRM	Selective progesterone receptor modulator
SSP	Swedish Universities Scale of Personality
SSRIs	Selective Serotonin Reuptake Inhibitors
STAI	State Anxiety Inventory
TE	Echo time
TFCE	Threshold free cluster enhancement
TP	Temporal Pole
TR	Repetition time
TBSS	Tract-based spatial statistics
UPA	Ulipristal acetate
VBM	Voxel-based morphometry
VN	Visual NETWORK

Introduction

The female menstrual cycle and the brain

During her life trajectory, a woman usually goes through hormonal transition periods and states, such as during puberty and the menopause. During the reproductive years, in the absence of use of hormonal contraceptives, variation in hormonal states occurs within shorter time periods as a result of ovarian hormone fluctuation, namely throughout the menstrual cycle. Of relevance to neuroscience, there is an increasing interest in the interaction between ovarian hormones and neural function and structure in women (COMASCO AND SUNDSTROM-POROMAA 2015; BELTZ AND MOSER 2020). To begin with, the menstrual cycle constitutes a brain, pituitary, and ovary interplay, which is approximately one month in duration (BECKER *et al.* 2002). The gonadotropin releasing hormone (GnRH), a tropic peptide hormone synthesized in the hypothalamus, is responsible for the release of gonatotropins, namely the luteinizing hormone (LH) and follicle-stimulating hormone (FSH), from the anterior pituitary to stimulate steroid production in the ovary (BECKER *et al.* 2002). The follicular phase is the stage leading to ovulation, characterized by increasing oestradiol levels that reach a peak before ovulation. Oestradiol promotes GnRH release, which in turn leads to the LH surge associated with ovulation (BECKER *et al.* 2002). During the post-ovulatory period, namely the luteal phase, progesterone levels increase and peak during the mid-luteal phase, with oestradiol levels following a similar pattern with a smaller peak. After this, progesterone and oestradiol levels continue to decrease until the end of the luteal phase, which is then followed by the onset of menstrual bleeding (ABRAHAM *et al.* 1972).

Ovarian hormones exert influence on the central nervous system (CNS) through the classical nuclear receptors, as well as non-classical membrane receptors, all expressed in several regions involved in cognitive function and emotional processing, such as the fronto-cortical, hypothalamic, hippocampal, and cerebellar structures (GUENNOUN 2020). In females, high progesterone and oestradiol receptor concentrations have been documented by human post-mortem and animal studies in key regions in affective processing, such as the amygdala, hypothalamus, and cerebellum, (BIXO *et al.* 1997; GUNDLAH *et al.* 2001; ÖSTERLUND AND HURD 2001; MITRA *et al.* 2003). In fact, one of the mechanisms by which oestradiol and progesterone influence behaviour and physiology is by functioning as transcription factors and as such by enhancing

or diminishing the expression of target genes (TETEL AND ACHARYA 2013). On the other hand, the neuromodulatory effects of ovarian hormones on neurotransmission can either impact the postsynaptic receptor responsiveness or the presynaptic synthesis, release, and transport of the neurotransmitter (MCEWEN AND PFAFF 1985; GENAZZANI *et al.* 2000; GARCIA-SEGURA *et al.* 2001; YANKOVA *et al.* 2001). While most research has focused on the effects of oestradiol on neurotransmission (BARTH *et al.* 2015), the role of progesterone alone or in interaction with oestradiol has only been recently investigated, pointing to relevant relationships with serotoninergic, glutamatergic, and dopaminergic neurotransmission (PLETZER *et al.* 2023). Thus, in regularly cycling women, ovarian hormones have the potential to dynamically modulate brain function in regions relevant to emotion and cognitive processing, as well as their structure (BIXO AND BÄCKSTRÖM 1990; BIXO *et al.* 1995; BIXO *et al.* 1997; DUBOL *et al.* 2021).

Premenstrual Dysphoric Disorder

Menstrually related mood disorders are a common cause of distress among women of reproductive age, recognized as a significant issue for nearly a century (HALBREICH 1993). These disorders are characterized by the presence of physical and affective symptoms, emerging during the luteal phase of the menstrual cycle and subsiding shortly after menses (HALBREICH 2004). Up to 20% of women of reproductive age report clinically relevant cyclical affective and physical symptoms during the luteal phase of ovulatory menstrual cycles (BORENSTEIN *et al.* 2003). A significant percentage (5%) presents more severe premenstrual suffering, known as premenstrual dysphoric disorder (PMDD), which can cause severe impairment in their everyday life and interpersonal relationships (HALBREICH 2003; EPPERSON *et al.* 2012; A.P.A. 2013). Recent evidence has highlighted the increased suicidal risk among PMDD sufferers (OSBORN *et al.* 2021; WIKMAN *et al.* 2022). Common PMDD symptoms include marked irritability, anger or interpersonal conflicts, depressive mood, anxiety, mood lability, somatic complaints, decreased attentional control, fatigue, and food cravings (Figure 1). The presence of at least one of these symptoms is essential for diagnosis. Even though those symptoms partly overlap with those of other mood disorders (YONKERS 1997), PMDD is a sex-specific disorder, characterized by cyclical symptom occurrence that leads to a great degree of suffering, reduced academic or professional performance, and social interactions, but that subsides upon menstruation (A.P.A. 2013). Symptom onset most often occurs during the early or mid-luteal phase. For most sufferers, it reaches a zenith in the late-luteal phase (Figure 2) and ceases shortly after the onset of menses (BÄCKSTRÖM *et al.* 2003; HARTLAGE *et al.* 2012; SCHMIDT *et al.* 2017). Despite the dearth of literature in this area, slightly variable symptom on- and off-set timing and duration have been proposed,

suggesting that there might be different PMDD temporal subtypes (DITZEN *et al.* 2020). Because no differences in the absolute hormonal levels are seen between PMDD women and healthy controls (BÄCKSTRÖM *et al.* 2003) and because the variation in oestrogens alone during the follicular phase is well tolerated, a prevalent hypothesis posits, as the trigger, altered neural susceptibility to the fluctuations of progesterone alone or together with oestrogens (BÄCKSTRÖM *et al.* 2003; SUNDSTROM-POROMAA *et al.* 2020).

Premenstrual Dysphoric Disorder DSM-5 Diagnostic criteria
A. In the majority of menstrual cycles, at least five symptoms must be present in the final week before the onset of menses, start to improve within a few days after the onset of menses, and become minimal or absent in the week postmenses.
B. One (or more) of the following symptoms may be present:
1. Marked affective lability (e.g. - mood swings, feeling suddenly sad or tearful, or in creased sensitivity to rejection)
2. Marked irritability or anger or increased interpersonal conflicts
3. Marked depressed mood, feelings of hopelessness, or self-deprecating thoughts
4. Marked anxiety, tension, and/or feelings of being keyed up or on edge
C. One (or more) of the following symptoms must additionally be present, to reach a total of five symptoms when combined with symptoms from Criterion B above:
1. Decreased interest in usual activities (e.g. - work, school, friends, hobbies).
2. Subjective difficulty in concentration
3. Lethargy, easy fatiguability, or marked lack of energy
4. Marked change in appetite; overeating; or specific food cravings
5. Hypersomnia or insomnia
6. A sense of being overwhelmed or out of control
7. Physical symptoms such as breast tenderness or swelling, joint or muscle pain, a sensation of "bloating," or weight gain
Note: The symptoms in Criteria A-C must have been met for most menstrual cycles that occured in the preceding year.
D. The symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships with others (e.g., avoidance of social activities; decreased productivity and efficiency at work, school, or home).
E. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, persistent depressive disorder (dysthymia), or a personality disorder (although it may co-occur with any of these disorders).
F. Criterion A should be confirmed by prospective daily ratings during at least two symptomatic cycles. (Note: The diagnosis may be made provisionally prior to this confirmation.)
G. The symptoms are not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or other medical condition (e.g., hyperthyroidism).

Figure 1. The DSM-5 diagnostic criteria for premenstrual dysphoric disorder (A.P.A. 2013)

The issue of how PMDD emerged is still unresolved. From an evolutionary perspective, there are various accounts regarding the origin of premenstrual symptoms. One of them is the possibility that symptoms entail an evolutionary advantage, as they would lead to abandoning an incompatible partner (GILLINGS 2014). In that sense, negative affect, irritability, and intense physical symptoms could serve to promote sexual avoidance. However, it is ultimately not necessary that certain phenotypes are always adaptive. It is important to consider that, during the past few thousand years, lifestyle and social

organization have radically changed from what they used to be, accompanied by changes in gender roles and reproductive habits. Women used to become sexually active and have their first pregnancy shortly after their first menses, while also having several children. On average, menopausal age used to occur much earlier than it does today, which was also related to the longevity of women and thought to provide an adaptive advantage (PERLS AND FRETTS 2001). Therefore, it is plausible to assume that the female brain has not had time to adapt to these relatively rapid societal changes (GREENE AND DALTON 1953).

To further understand the pathophysiology of PMDD, candidate gene studies have sought to reveal associations between genetic variations and PMDD. Links between the neural susceptibility in PMDD and genetic factors have also been revealed, that is, altered Extra Sex Combs/Enhancer of Zeste complex gene function (DUBEY *et al.* 2017), polymorphisms in the oestrogen receptor alpha gene (HUO *et al.* 2007) and 5-hydroxytryptamine transporter 1A gene (GINGNELL *et al.* 2010). Nevertheless, studies have also failed to demonstrate significant evidence of the involvement of the 5-hydroxytryptamine gene polymorphism, serotonin-transporter-linked promoter region, as a potential genetic marker for the disorder (MAGNAY *et al.* 2010; COMASCO *et al.* 2014).

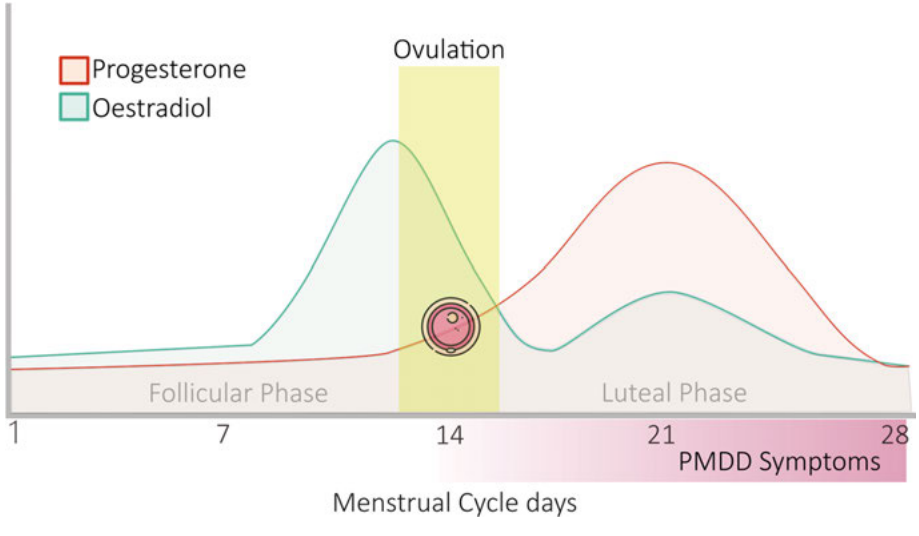

Figure 2. Progesterone and oestradiol fluctuations throughout the menstrual cycle and PMDD symptom occurrence in the luteal phase.

Regarding symptom occurrence, the literature indicates that it is likely triggered by ovulation (HALBREICH 2003). Hormonal manipulation by use of GnRH agonist-induced ovarian suppression has been associated with the ceasing of the luteal-phase-related negative symptoms (SCHMIDT *et al.* 1998; SUNDSTRÖM *et al.* 1999) and their reoccurrence after ovarian hormone

replacement (SCHMIDT *et al.* 1998). Nevertheless, the distinct effects of the two hormones on premenstrual negative affect in PMDD are yet to be determined.

Treatment alternatives do exist, but there is a scarcity of literature on their efficacy and mechanistic signatures. Selective serotonin reuptake inhibitors (SSRIs) are presently considered the primary treatment choice, showing a moderate to high response rate irrespective of continuous or intermittent (luteal-phase) administration, especially in addressing mood symptoms (MARJORIBANKS *et al.* 2013). Common SSRI side effects have been shown to lead to treatment interruption (SUNDSTRÖM-POROMAA *et al.* 2000). In cases of response failure to SSRIs, hormonal regulation treatments are available, such as combined oral contraceptives, and GnRH agonists. Studies on hormonal interventions have employed diverse methods, making them not always comparable, and are generally not prospective. Existing evidence on combined oral contraceptives has demonstrated mixed response outcomes, and hormonal interventions are also associated with a high risk of mood disturbance development (RAPKIN *et al.* 2019; SUNDSTRÖM-POROMAA AND COMASCO 2023). This risk has been shown to depend on factors such as the dose, compound, or the individual's psychiatric vulnerability (RAPKIN *et al.* 2019). Regarding GnRH interventions, treatment efficacy is reported to be generally high, due to ovarian suppression, which is thought to be a prerequisite for symptom appearance. However, progesterone and oestradiol addback is necessary and is also known to induce symptom reinstatement (SCHMIDT *et al.* 2017), rendering long-term administration challenging. Allopregnanolone, a progesterone downstream derivative, seems to be instrumental in premenstrual symptomatology, due to its actions as a positive allosteric modulator of GABA (gamma-aminobutyric acid)-A receptors (BÄCKSTRÖM *et al.* 2014). Its interaction with serotonergic receptors is further thought to be part of the mechanism of action of SSRIs (SUNDSTROM-POROMAA *et al.* 2020; SIKES-KEILP AND RUBINOW 2023). In this light, 5α-reductase inhibitors, which act by hindering the allopregnanolone conversion from progesterone – or pregnanolone, an allopregnanolone inhibitor – are suggested as promising treatment alternative (SUNDSTRÖM-POROMAA AND COMASCO 2023), after being preliminarily shown to alleviate PMDD symptoms (MARTINEZ *et al.* 2016; BIXO *et al.* 2017). Nevertheless, the latter alternatives are not approved treatments and further research is warranted. Other treatment options are cognitive behavioural interventions, with specific focus on emotion regulation and coping strategies, although efficacy evidence is limited and reviews have focused on comparing psychological treatments with SRRIs (HANTSOO AND EPPERSON 2015).

Progesterone and selective progesterone receptor modulators

Progesterone is highly lipophilic and can readily pass through the blood-brain barrier (BIXO *et al.* 1995; BIXO *et al.* 1997). The temporal link between symptom occurrence and progesterone fluctuations has rendered this hormone a potential trigger of symptom occurrence (WYATT *et al.* 2004). More specifically, symptom emergence can occur immediately after ovulation, and the severity usually increases during the luteal phase, as serum progesterone levels fluctuate (BÄCKSTRÖM *et al.* 2014). Two earlier clinical trials on small samples investigated the effects of mifepristone treatment on PMDD symptom severity (SCHMIDT *et al.* 1991; CHAN *et al.* 1994). This is a progesterone receptor antagonist used mostly for early pregnancy termination owing to its ability to block progesterone action in the uterus. One study found that progesterone antagonism did not have any effect on symptom timing or length (SCHMIDT *et al.* 1991), although one demonstrated symptom improvement at a non-statistically significant level (CHAN *et al.* 1994). However, these results cannot determine non-efficacy, as in one of these studies the treatment was administered too late in the menstrual cycle to induce anovulation (SCHMIDT *et al.* 1991), while the other lacked statistical power owing to the rather small sample size (CHAN *et al.* 1994).

Historically, antiprogestins have been used for several purposes, including contraception and hormone-related conditions (ATTARDI *et al.* 2002). This class of synthetic steroids interacts with the progesterone receptors and can exert agonistic and antagonistic properties in a tissue-specific, cell-specific, and physiologically specific manner (RABE *et al.* 2018). The action profile of selective progesterone receptor modulators (SPRMs) depends on theirstructure and the availability of coregulators, namely the nuclear proteins impacting transcription function in the nuclear receptors of the target cell (BOUCHARD *et al.* 2011) (Figure 3). Ulipristal acetate (UPA) belongs to the new class of SPRMs that is primarily used in higher doses for emergency contraception (BRACHE *et al.* 2013), and in low dosages as treatment for uterine fibroids (CROXTALL 2012). UPA can inhibit ovulation, provided that the luteinizing hormone (LH) surge has not already begun (GEMZELL-DANIELSSON AND MENG 2010). It mainly exerts antagonistic action on the progesterone receptor in different tissues (WHITAKER *et al.* 2014) by prohibiting circulating progesterone to bind the receptor and thus impacting progesterone metabolism and transcription (KEENAN 2011; RABE *et al.* 2018). As opposed to other antiprogestins, such as mifepristone, UPA has significantly less antiglucocorticoid activity (MELIS *et al.* 2012), making it more appropriate for long-term treatment. In low-dosage regimens, even though UPA has inhibitory effects on the progesterone receptor, it maintains oestradiol levels at mid-follicular levels, along with inducing anovulation in most women (CHABBERT-BUFFET *et al.* 2007; WHITAKER *et al.* 2014; CHABBERT-BUFFET *et al.* 2018). Recently,

compared with a placebo, daily treatment with 5mg UPA for 3 consecutive months was associated with a two-fold reduction of PMDD symptoms including marked irritability, anger and depressive symptoms, as demonstrated in the first randomized, double-blind, controlled study on individuals with PMDD (COMASCO *et al.* 2021). In line with this, one study found beneficial effects of UPA, on the same dosage regimen, on self-reported premenstrual symptoms in women undergoing treatment for uterine leiomyomas with comorbid premenstrual syndrome (CHEN *et al.* 2017). This is not the first time hormonal treatments have successfully been used in female-specific psychiatric disorders, considering the recently approved use of brexanolone, a synthetic formulation of allopregnanolone, for postpartum depression (MELTZER-BRODY *et al.* 2019). However, the mechanism by which UPA treatment precipitates symptom relief in PMDD is far from completely understood.

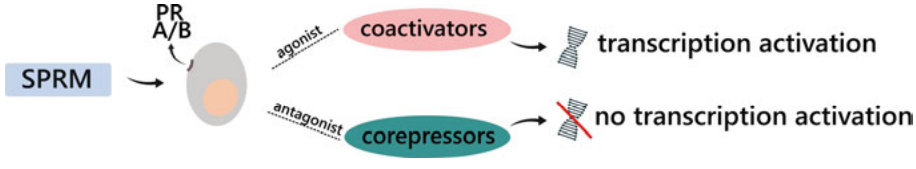

Figure 3. Selective progesterone receptor modulator mechanism. SPRMs interact with the progesterone receptor through coactivators or corepressors and exert either agonistic (and thus activate gene transcription) or antagonistic effects that cause gene down-regulation.

Ovarian hormone actions on the brain and genes

Ovarian steroid hormones have become increasingly central in psychopharmacology since the early nineties, owing to their ability to regulate a number of functions in the central and peripheral nervous system, including neuroendocrine functions and behaviour (BARTH *et al.* 2015). One of the earliest and most prominent findings on the impact of ovarian hormones revealed that sexual behaviour was mediated by steroid receptors in the hypothalamus (DAVIS *et al.* 1979; PFAFF 1979).

The marked influence of ovarian hormones varies depending on the type of cells. A few of oestradiol's actions include cycle-related effects on hypothalamic regions, proliferative effects on Schwan cells in the brain's cortical and subcortical regions, along with inducing progesterone synthesis in astrocytes (GARCIA-SEGURA AND MELCANGI 2006). Similarly, progesterone has multiple actions on glia cells, such as reducing microglial proliferation, as indicated by cell cultures. A number of *in vivo* rat and primate studies have noted the neuroprotective effects of oestradiol including synaptic remodelling and synaptogenesis in regions such as the hippocampus, hypothalamus, and the

prefrontal cortex (PFC) (WOOLLEY AND MCEWEN 1993; MCEWEN 2002; TANG *et al.* 2004; MACLUSKY *et al.* 2005). In rodents, progesterone and its metabolites have been shown to be involved in microglia release (ZWAIN AND YEN 1999; MULLER AND KERSCHBAUM 2006) and myelin production, according to cell culture findings (SCHUMACHER *et al.* 2000).

Studies have also demonstrated the plasticity effects of progesterone (CAMACHO-ARROYO *et al.* 2020). Both oestradiol and progesterone have been shown to have oestrus cycle effects on dendritic spine density, as demonstrated by rodent studies (CAMACHO-ARROYO *et al.* 2020). For instance, progesterone has been positively related to dendritic spine increase in the cerebellar Purkinje cells of rat pups, while the effect was absent upon mifepristone administration (SAKAMOTO *et al.* 2002). In extrahypothalamic regions, progesterone was shown to have proliferation and neuroprotective effects, such as promoting the Schwann cell myelinating program, along with a regulatory function on oestrogenic receptors, as shown in rat and primate studies (BRINTON *et al.* 2008). In humans, organizational effects of progesterone and oestradiol have been documented in young adulthood in sexual dimorphic areas (WITTE *et al.* 2010). Furthermore, both oestradiol- and progesterone-dependent cyclic effects on subcortical grey matter have been found, potentially implicated in menstrual-cycle related cognitive and emotional changes (PLETZER *et al.* 2018; DUBOL *et al.* 2021).

Evidence on the neurotrophic effects of steroid hormones has also been provided, such that in the rat hippocampus, among other regions, there is an impact of primarily oestradiol, but also progesterone, on the brain-derived neurotrophic factor (BDNF) mRNA and protein (SINGH *et al.* 1995; GIBBS 1999). BDNF is central to neurogenesis, neural survival, and differentiation (BATHINA AND DAS 2015), while a functional oestrogen response element has been found in the gene encoding BDNF, suggesting oestrogen-mediated neuroprotection (SOHRABJI *et al.* 1995). Interestingly, a functional neuroimaging study demonstrated that having the less functional variant of a common polymorphism in the BDNF gene is associated with lower activation of frontocortical regions while processing emotional stimuli during the late luteal phase in women with PMDD compared with healthy controls (COMASCO *et al.* 2014). It is therefore possible that genetic predisposition contributes to the neural susceptibility to ovarian hormones in PMDD.

Irritability and aggression

Irritability and anger are described as the main and perhaps the most burdensome symptoms of PMDD (ERIKSSON *et al.* 2002; RAPKIN AND WINER 2009). Irritability, aggression, and oftentimes hostility that lead to conflicts, constitute characteristics of a wide range of psychopathologies in the realm of mental health and specifically among mood disorders, including depressive and

bipolar as well as anxiety disorders (SAFER 2009; YAGER 2020), although it is more prominent in PMDD (LANDÉN AND ERIKSSON 2003). Classical theories in psychology and behavioural sciences have defined irritability as exaggerated reactivity to emotion-ridden, predominantly negative, stimuli and provocations (LEIBENLUFT 2017). One potential outcome of irritability is aggressiveness (VIDAL-RIBAS *et al.* 2016). In past attempts to define the neural correlates of reactive aggression as a main symptom of disorders, such as intermittent explosive disorder and borderline personality disorder, the prevalent idea is the altered relationship between control of the top-down control cortical regions (prefrontal, orbitofrontal cortex) and mesolimbic emotion processing regions, such as the amygdala (COCCARO *et al.* 2007; GAN *et al.* 2016).

One of the instruments used to assess reactive aggression is the point subtraction aggression paradigm (PSAP), a tool that has been validated as a functional magnetic resonance imaging (fMRI) paradigm (KOSE *et al.* 2015). PSAP comprises choices between monetary reward and costly punishment through provocations, thus allowing us to target affective misbalance in impulsive aggression and emotion processing in relation to inhibitory capacity (SIEVER 2008). In healthy subjects, increased activation after receiving provocation has been seen in brain regions implicated in emotion, reward processing and cognitive control, while performing the PSAP task (i.e., the amygdala, striatum, medial orbitofrontal cortex (OFC), PFC, and ACC) (SKIBSTED *et al.* 2017).

Previous findings indicate sex differences in aggression as well as the impact of ovarian hormones on female aggression, albeit inconclusively. Older research has suggested differences in aggressive behaviour between sexes (CAMPBELL 1999; LAHEY AND WALDMAN 2003). When investigating sex differences in reactive aggression with an event-related potential study – an electroencephalography technique measuring indexes of, among other things, cognitive events – enhanced frontal negativity during the punishment decision upon provocation was reported regardless of sex (KRÄMER *et al.* 2008). In healthy women, high luteal progesterone levels have been negatively associated with aggression and irritability (ZIOMKIEWICZ *et al.* 2012), as well as with amygdala reactivity to negative stimuli and its functional connectivity with the medial PFC (mPFC) (VAN WINGEN *et al.* 2008).

Overall, the evidence on menstrual cycle effects on aggression is inconclusive. Older findings suggest that greater irritability levels have been found to be related to lower allopregnanolone levels in the luteal phase when compared with women demonstrating lower severity in irritability (GIRDLER *et al.* 2001). According to another earlier study, self-reported physical aggression was found to be higher during menses than in the mid-luteal phase in young women (RITTER 2003). A study assessing relationships between hormones and aggression found positive associations between follicular oestradiol levels and verbal aggression, along with a negative correlation between luteal

progesterone and hostility (BRAMBILLA *et al.* 2010). The association between testosterone and aggression is well researched in men, but the literature notes a weaker relationship in women (DENSON *et al.* 2018). A more recent study assessing the relationship between reactive aggression and testosterone levels in healthy women, using an ultimatum task, provided evidence of higher testosterone relating to higher reactive aggression (PROBST *et al.* 2018). In general, high arousal symptoms such as irritability are typical in reproductive mood disorders (FREEMAN *et al.* 2011; EISENLOHR-MOUL *et al.* 2017), with the symptom being a common denominator among disorders with cyclical symptomatology, such as bipolar personality disorder (EISENLOHR-MOUL *et al.* 2018).

Regarding irritability as a symptom of PMDD, its neural correlates are widely unexplored, thus no inferences can be made concerning whether the brain circuits underlying PMDD irritability are similar to those underlying other affective disorders. Notably, irritability, along with depressive symptoms, showed the most significant improvement in a recent proof of concept clinical trial using SPRM compared with a placebo (COMASCO *et al.* 2021). Taken together, the marked irritability observed in the luteal phase of women with PMDD could be the result of impaired cognitive control (cortico-limbic, top-down inhibitory control) on exaggerated emotional response.

Functional and structural neuroimaging evidence in PMDD

Psychological studies have found evidence supporting the impact of dysfunctional emotional and cognitive responses on the temporal frame and intensity of premenstrual suffering (DAWSON *et al.* 2018). The neural correlates of PMDD have been studied sparsely, and most of the neuroimaging literature comprises fMRI studies with a predominant interest in emotion regulation or processing (DUBOL *et al.* 2020). Menstrual-cycle-phase- and symptom-related altered brain activation has been reported in PMDD, with general limbic hyperresponsiveness to negative stimuli and diminished activity in the medial and dorsal prefrontal and orbitofrontal regions, along with the emotional regulation network involving the anterior cingulate cortex (ACC) (DUBOL *et al.* 2020).

A definitive relationship between top-down network dysfunction and emotional regulation as the basis of PMDD symptomatology has yet to be established, as there is only sparse evidence supporting this hypothesis (DUBOL *et al.* 2020). Interestingly, while some functional neuroimaging studies investigating cognitive control and emotion processing have failed to report luteal phase amygdala reactivity differences in women with PMDD compared with controls or between menstrual phases in PMDD patients (GINGNELL *et al.*

2012; GINGNELL *et al.* 2013; PETERSEN *et al.* 2018), two studies have found increased luteal amygdala response in patients compared with controls (PROTOPOPESCU *et al.* 2008; GINGNELL *et al.* 2014). Additionally, an association between luteal amygdala reactivity to emotional cues and high trait anxiety levels seems to hold true in individuals with PMDD compared to healthy women (GINGNELL *et al.* 2012). Moreover, the stimuli in each study were slightly different, and only in the Gingnell et al. (2012) study did the stimuli have social relevance and not simply emotional valence (GINGNELL *et al.* 2012). Additional evidence showed decreased dorsolateral PFC response to an emotion regulation task during the luteal phase (PETERSEN *et al.* 2018). Blunted fronto-cingulate response to negative emotional face matching was found both in the follicular and in the luteal phases and was also related to the *BDNF* Val66Met polymorphism (COMASCO *et al.* 2014). Conversely, in a study using the classic working memory n-back task, Baller and colleagues revealed enhanced prefrontal activation across different hormonal states, which correlated with PMDD-related disability and duration of illness (ERICA B. BALLER *et al.* 2013). When assessing response inhibition, individuals with PMDD exhibited diminished parietal activity in either the follicular or luteal phases (BANNBERS *et al.* 2012). Consequently, despite the findings supporting a hypothesis of aberrant cortico-limbic activity in the symptomatic phase (DUBOL *et al.* 2020), the variable direction of results in certain of the aforementioned studies could imply generalized alterations in emotional processing in PMDD women. Most recently, during increased luteal-phase-specific activation in attention-relevant cortical regions was observed, during emotional face processingwhile differential subcortical activation was positively associated with luteal isoallopregnanolone/allopregnanolone ratios (STIERNMAN *et al.* 2023).

With regard to negative stimulus anticipation, luteal-phase reactivity of the medial and dorsolateral prefrontal cortex, key regions in the control network, was greater in PMDD women compared to healthy controls (GINGNELL *et al.* 2013). However, another hypothesis postulates that PMDD symptoms are more socially oriented, which is a possible explanation for the lack of amygdala reactivity in some studies, as the study designs were not related to social context. A study by Gingnell and colleagues (GINGNELL *et al.* 2014) investigated social emotional stimuli in assessing luteal phase affective processing and confirmed phase-related enhanced amygdala and insula but attenuated anterior cingulate reactivity to social stimuli in the clinical population. Altogether, most evidence on PMDD points to a prefrontal control network deficit in efficiently regulating the subcortical regions, implicated in emotional processing during the symptomatic phase.

The literature on functional brain connectivity at rest provides a less coherent account (DUBOL *et al.* 2020). Syan and colleagues were the first to explore resting state functional connectivity (rs-FC) across the menstrual cycle in individuals with PMDD, reporting no significant differences between PMDD

women and controls (SYAN *et al.* 2018). More recently, two studies explored the same in PMDD populations as compared to controls using different methods (PETERSEN *et al.* 2019; DAN *et al.* 2020). Petersen and colleagues demonstrated menstrual-cycle-phase-independent differences between cases and controls, showing specifically enhanced temporal connectivity to the executive control network as well as higher amygdala-prefrontal connectivity in the follicular phase for the PMDD group (PETERSEN *et al.* 2019). Employing graph theory, Dan and colleagues observed decreased functional network segregation and increased functional network integration for the PMDD sample, along with diminished within-network connectivity in the temporal lobe and thalamic and basal ganglia hyperconnectivity regardless of phase (DAN *et al.* 2020). Taken together, this preliminary literature suggests altered PMDD-specific functional network dynamics including cortical and subcortical regions.

Even though differential hemodynamic responses in individuals with mood disorders compared to controls coincide with structural changes (DREVETS *et al.* 2008), to the best of our knowledge, structural brain signatures in PMDD are far from established. In healthy women, there is some evidence on the menstrual-cycle-related impact of ovarian hormones on brain structure, in regions such as the hippocampus, amygdala, and prefrontal cortex (DUBOL *et al.* 2021). Despite the limited available evidence in the literature, oestradiol-dependent grey matter volume alterations have been found in the insula (DE BONDT *et al.* 2016) and hippocampus (BARTH *et al.* 2016), while both oestradiol (LISOFSKY *et al.* 2015) and progesterone (DE BONDT *et al.* 2016) were linked to cerebellum volume. Regarding PMDD, only a few studies have focused on the anatomical brain correlates underlying the disorder, and the findings are rather inconclusive (DUBOL *et al.* 2020). Recently, altered structural correlates emerged from data-driven evidence striving to distinguish PMDD women from controls, with specifically smaller cerebellar, amygdala, putamen, and ventral posterior cortex grey matter volumes, as well as lower cortical thickness throughout the fronto-cingulate and temporal cortical regions (DUBOL *et al.* 2022a). Furthermore, in another study, the severity of depression was negatively associated with amygdala grey matter volume, while additional symptoms were found to be related to other cortical surface measures (DUBOL *et al.* 2022b). Lastly, the only study investigating white matter as a potential biomarker for PMDD revealed differential white matter volume and fractional anisotropy (FA) in the limbic tract connecting temporo-frontal regions, the uncinate fasciculus, which was higher in the PMDD group compared to controls (GU *et al.* 2022). Therefore, it is important to investigate whether morphological changes are part of the disorder and SPRM treatment response.

Aims

Study I

The psychoneurobiological signatures of SPRM treatment in relation to aggression were investigated by having PMDD women perform the PSAP task while their brain was scanned using functional magnetic resonance imaging. The scope of this study was to assess whether SPRM treatment compared with placebo would be associated with differential neural activation during a reactive aggression task. Functional connectivity patterns as a response to the provocation and aggressive response conditions were additionally investigated. Also assessed were symptom severity, aggressive behaviour during the task, and state aggression differences compared between groups and evaluated in relation to brain reactivity.

Differential brain reactivity between the two treatment groups were expected in cortical and subcortical structures for the provocation and aggressive response conditions. Enhanced top-down control and fronto-limbic connectivity were hypothesized for the women receiving SPRM treatment compared with a placebo. Moreover, the study aimed to explore the relationship between BOLD signal and symptom severity, task-related aggressive behaviour, ovarian hormones, and psychometric scores. Reduced symptom severity and lower aggression scores were expected to relate to improved top-down control, reflected in enhanced cortical and reduced subcortical activation, in the treatment group. Similarly, women receiving SPRM were hypothesized to demonstrate less aggressive behaviour upon provocation compared to the placebo group.

Study II

The effect of SPRM treatment on grey matter volume and cortical surface architecture was investigated in women with PMDD. We assessed grey matter volume and cortical surface measures before and during the last treatment cycle with SPRM, compared with a placebo. Specifically, the interaction effect of time by treatment on grey matter volume and cortical surface was assessed both by employing an exploratory whole brain approach and by focusing on the regions of interest hypothesized to be related to PMDD. Furthermore, we tested whether potential changes in brain structure were associated with

symptom improvement. Despite the limited and inconsistent literature on the structural brain correlates of PMDD, we hypothesized that SPRM treatment would impact brain structure in the cortical and subcortical regions, but no direction was hypothesized due to the dearth of relevant literature. In line with this, potential changes in grey matter and surface were expected to be correlated with a decrease in symptom severity.

Study III

Diffusion tensor imaging was used to explore potential alterations of white matter integrity before and after treatment with SPRM compared with a placebo. Due to the lack of white matter integrity correlates in PMDD, an exploratory whole-brain approach was employed. The longitudinal effect of time by treatment on the four diffusion metrics (FA, mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD)) was considered the primary outcome with regard to treatment effect.

As a secondary outcome, treatment group comparisons were tested for the follow-up timepoint. Additionally, correlations between change in white matter integrity and change in symptom severity from baseline were carried out. No directional hypotheses were posited.

Study IV

Potential white matter signatures of SPRM treatment when compared with a placebo were investigated by looking into white matter volume. The treatment by time interaction effect on white matter volume was assessed voxel-wise. Both exploratory whole-brain and regions of interest analyses were employed, using previously defined regions (GU *et al.* 2022) for the latter. Differences between the treatment groups were also estimated in each timepoint (baseline and follow-up), and timepoint differences were investigated for each treatment group.

Study V

Functional resting state network connectivity was explored in relation to SPRM treatment in our PMDD sample, which was randomized to either active treatment or placebo. The treatment by time effect on functional connectivity was tested, first by using regions that are parts of the classic resting state functional networks as seeds and additionally by using the functional cluster from a previous paper as a seed (KALTSOUNI *et al.* 2021).

Post-hoc analyses were done on the significant interaction clusters to further specify the direction of the time and treatment group differences. Additionally, correlations between the change in functional connectivity and change in symptom severity and hormonal levels from baseline to follow-up were tested. Due to limited functional connectivity evidence in relation to PMDD, no specific hypotheses were posed.

Methods

Participants and study Design (All studies)

The samples in the five neuroimaging sub-studies included in this thesis are subsets of the participants involved in the double-blind, placebo-controlled clinical trial, who consented to participate in the neuroimaging study (COMASCO *et al.* 2021). Study procedures were approved by the ethics committee of Uppsala (Dnr. 2016/184) and the Medical Products Agency in Sweden, EUDRA-CT 2016-001719-19. Women with a PMDD diagnosis according to DSM-5 criteria were included. Diagnosis was confirmed by daily prospective symptom ratings during two consecutive menstrual cycles with the Daily Report Severity of Problems (DRSP) scale (ENDICOTT *et al.* 2006b). Following the diagnostic procedures, in the luteal phase of the baseline cycle, all subjects: i) filled out a battery of questionnaires on mood and personality; ii) underwent blood sampling, iii) a structural brain scan, a resting state fMRI scan, and a DTI scan. Scanning was scheduled in the luteal phase of the baseline cycle. At baseline, participants were randomized to either SPRM or placebo and were instructed to start taking the pills on the first day of menses. At follow-up, the same procedures were followed, and participants underwent their second scanning session during the final week of active SPRM or placebo treatment, with the addition of a BOLD fMRI scan while performing the PSAP task taking place at this timepoint. Primary outcome measures the influence of treatment on both brain structure and function and related changes in symptom severity.

Swedish speaking women with regular menstrual cycles between 18 and 46 years of age were eligible for participation in the study. Exclusion criteria were ongoing psychiatric disorders, ruled out by the use of the MINI International Neuropsychiatric Interview (SHEEHAN *et al.* 1998), hormonal contraceptive use, pregnancy or breast-feeding, psychotropic medication treatment, contraindication to magnetic resonance imaging, and other medical conditions. The design is summarized in figure 4.

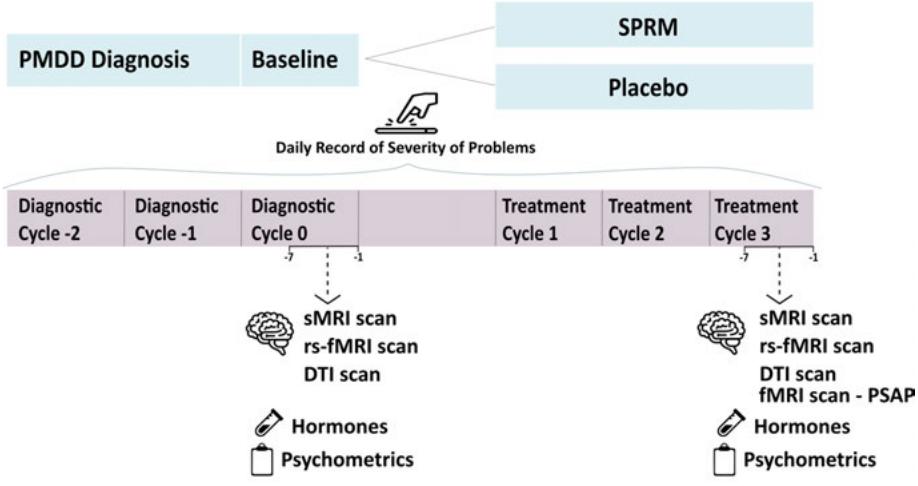

Figure 4. Screening phase and study design for the structural and functional MRI studies. DTI: diffusion tensor imaging, PMDD: premenstrual dysphoric disorder, SPRM: selective progesterone receptor modulator, sMRI: structural magnetic resonance imaging, fMRI: functional magnetic resonance imaging, PSAP: point subtraction aggression paradigm, rs-fMRI: resting state functional magnetic resonance imaging.

DRSP and Psychometric Scales (All studies)

The DRSP instrument constitutes a daily rating list of PMDD physical and psychological symptoms through 21 items scored on a 6-point severity scale, in the different phases of the menstrual cycle in order to confirm PMDD diagnosis (ENDICOTT *et al.* 2006a). Those items are grouped in 11 domains according to the symptom criteria on PMDD diagnosis, irritability/anger, depression, anxiety, affective lability, difficulties in concentration, lethargy, interest in activities, sleep, appetite, control, and physical symptoms (A.P.A. 2013). The instrument has been shown to have high validity and reliability in preliminarily assessing PMDD diagnosis. The scale is self-administered, ratings are done prospectively, for at least two consecutive menstrual cycles, and the items were initially designed to correspond to the DSM-IV criteria on PMDD symptomatology. Each item offers a 6-point categorical rating, in which severity is defined from 1, not at all, to 6, extreme.

Following the diagnostic procedures, in the luteal phase of the baseline month, all subjects filled out a battery of questionnaires on mood and personality (i.e. the Montgomery-Asberg Depression Rating Scale (MADRS), the State Anxiety Inventory (STAI), the Swedish Universities Scale of Personality (SSP), the Aggression Questionnaire-revised Swedish version AQ-RSV (ÅGREN 2001). The AQ-RSV scale is the Swedish adaptation of the e Buss–Durkee Hostility Inventory (BDHI) used for measuring the dimensions of

direct and indirect aggression. Regarding the personality parameters, the SSP scale was used, an instrument calibrated on Swedish population to measure the three main personality factors, neuroticism, aggressiveness, and extraversion (GUSTAVSSON *et al.* 2000).

Magnetic resonance imaging techniques (All studies)

The development and advancements of magnetic resonance imaging (MRI) have been groundbreaking for neuroscience research. MRI constitutes a non-invasive tool, allowing for *in vivo* observation of brain activity, dynamics, networks, and structural changes through an increasing number of sophisticated methods of data acquisition. The need to localize the brain structures and networks behind mental states and behavioral patterns has always been a major interest in philosophical, psychological, and biomedical research. In the late 1970s, Richard R. Ernst introduced the first system to turn radio-frequency signals into two or three-dimensional pictures, following the quantum theory orientations about the properties of observing atomic nuclei when exposed to strong magnetic fields (HUETTEL *et al.* 2004). Today, it is one of the most utilized and advanced methods in research and clinical applications and is rather eminent in deciphering the cognitive and emotional states, while providing good spatial and temporal resolution and multiple measurements over the entire brain (LOGOTHETIS 2008).

Generating images through an MR scanner is implemented by using deferent acquisition sequences and contrasts. Typically, a common contrast method is relaxation time (e.g. T_1, T_2, T_2*). T1 images are sensitive to the number of protons present within each voxel and is the overall measure of signal intensity, as protons are individually emitting signals, which leads to brightness in proton- rich areas. T1 contrast between gray and white matter, depends on the time interval between excitation pulses (repetition time- TR) and consists of T1 excitation and T1 relaxation; high contrast images are highly dependent on a shorter tissue T1 value, which means that the TR values would be longer and longitudinal magnetization has time to fully recover. Analogously, T2 contrast images have maximal signal in fluid- filled regions and show neurons' transition to a resting state; In T2- weighted images the amount of signal loss depends on the time between excitation and data acquisition, namely, the echo time (TE), so with a longer TE, there the signal would be smaller (HUETTEL *et al.* 2004). T2* images are deoxygenated hemoglobin- sensitive and produced by pulse sequences with long TR and intermediate TE values and is the main opponent of echo- planar imaging (EPI), a technique sensitive to magnetic field changes, allowing fast acquisition of two- dimensional image, through a voxel- by- voxel procedure.

A fundamental method researchers utilize to measure brain activity is the measurement of metabolic underpinnings of neuronal activity, which is called

blood- oxygenation- level dependent (BOLD) contrast (GAZZANIGA 2006). Briefly, neuronal activity leads to increase in blood flow and the supply of oxygen that exceeds oxygen demand in active regions, resulting in oxygenated hemoglobin increase in the neural tissue, displacing the deoxygenated hemoglobin and, therefore, increasing the BOLD signal intensity (HOGE *et al.* 1999). Since the late 1800s it has been observed that mental processing can be traced in changes in blood flow, based on which later research ensued, proving that neuronal signals are correlated to regional blood oxygenation and flow (HUETTEL *et al.* 2004). The word correlation is emphasized, as although the images are structured by the manipulation of protons' magnetic moments (Figure 5), these moments are too weak to be detected by fMRI, so the hemodynamic activity observed during an fMRI scan is a correlational proxy of the actual neuronal activity.

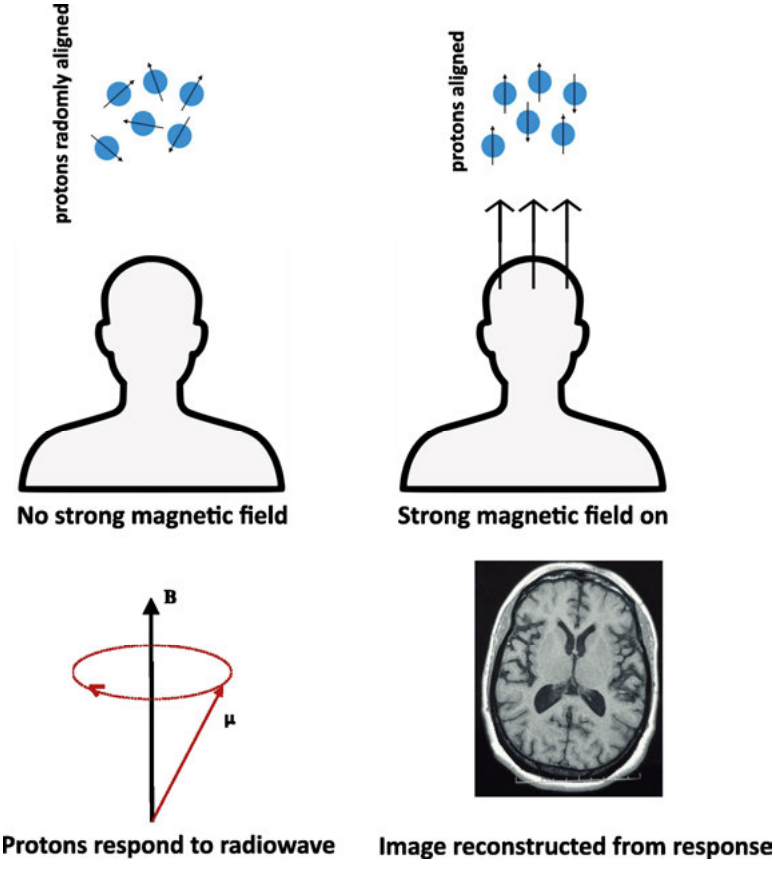

Figure 5. When no strong magnetic field is present, the protons are randomly aligned. Proton alignment occurs in the presence of a strong magnetic field (B_0). When the protons align with the magnetic field, a net magnetic moment is produced (μ) parallel to B. The proton's response is what is reconstructed in the produced image.

Since energy is not stored in neurons, their firing due to stimulation leads to metabolic changes, as blood flow quickly increases in order to fulfill the neurons' energy demands (MAGISTRETTI AND PELLERIN 1999). Hemoglobin molecules are bound in red blood cells, which molecules have different magnetic properties depending on whether the oxygen molecules bound on their heme proteins were released or not; with still bound oxygen, hemoglobin is called diamagnetic and has limited magnetic field effect, in contrast to the paramagnetic one, which means it has released its oxygen, leading to magnetic field concentration. The latter is the main element of MR images produced by the BOLD contrast technique, as the contrast depends on the changes in deoxyhemoglobin concentration, based on which researchers make inferences on brain function. The amount deoxygenated hemoglobin concentration is a proxy measure of the balance between oxygen consumption and supply during a process, with the former depending on neural activity and the latter on blood flow (PAULSON *et al.* 2010). While the amount of deoxygenated hemoglobin decreases, the BOLD signal increases, and reversely. However, that happens because the oxygenated hemoglobin displaces the deoxygenated hemoglobin, which was suppressing the MR signal and not because itself propagates it. The BOLD contrast depicted in the images is comprised of proton density (pd) contrast, T1 contrast, T2 contrast and T2* weighted images.

Although BOLD signal acquisition has provided us with a non- invasive imaging method, that has extended the common knowledge on brain function, it is still an indirect means of inference on neural function, as also mentioned previously. For neurons to return to their original polarization state, glucose should be transported, which requires more blood. This increase in blood flow, also leads to oxygenated hemoglobin molecule increase and oxygen concentration is used in glucose-burning (HUETTEL *et al.* 2004). Those processes interfere with deoxygenated hemoglobin decrease, interfering less with magnetization. The glucose necessities- cerebral blood flow relationship varies across regions and it makes it more difficult to determine the neural correlates of mental function, as it depends on the vascular anatomy and spatial scale of blood- flow regulation; in higher cognitive function related areas, blood flow response is relatively higher than others, that have les inflow than consumption (HUETTEL *et al.* 2004). The sensitivity of the BOLD signal is a fair weakness and areas like that can affect it. Another example could be higher vascularization areas, like primary sensory cortex, that typically shows higher fMRI responses. Due to its high sensitivity, it is also prone to other factors. An additional difficulty is that the signal cannot distinguish feedforward to feedback active networks in a region, with both inhibitory and excitatory inputs being summed up in the BOLD signal.

Introduced in the late 90s, another advancement in functional neuroimaging is the concept of spontaneous BOLD activity. This term emerged after the observation of low frequency BOLD fluctuations in the primary sensory motor cortex without the presence of motor behavior (BISWAL *et al.* 1995) and

later became established as resting-state brain activation or resting-state functional connectivity. Resting state connectivity refers to the synchronous low frequency (<0.1 Hz) BOLD signal among regions (ROSAZZA AND MINATI 2011). Since then, several resting state networks have been recognized, with the most prominent being the default mode network (DMN), first characterized as the "default mode" brain activity when participants lie with their eyes closed (RAICHLE *et al.* 2001). The DMN is responsible for higher order self-referential thinking (FOX AND RAICHLE 2007). Since then, the field has been making continuous advancements in terms of resting state data analyses as well as preprocessing methodologies and, replicating cognitively and clinically relevant brain networks, such as the salience, central executive networks, amongst others (YANG *et al.* 2020).

Another type of MRI was born in 1985, namely diffusion-weighted imaging, which primarily focuses on the measurement of water diffusion along the neural fibers to characterize tissue structure *in vivo* (LE BIHAN 2012). More specifically diffusion tensor imaging (DTI) involves a diffusion model that allows for the measurement of four main parameters related to water diffusion along the white matter tracts of the brain. These parameters include FA, which represents the degree of directionality along myelinated tracts, as well as three measures of water molecule movement in relation to the tracts' geometry: mean diffusivity, axial diffusivity, and radial diffusivity (BASSER *et al.* 1994a; BASSER *et al.* 1994b; BASSER 1995). The metrics offer information about the disparities in diffusion, specifically how water moves in various directions, contingent on the type of tract, its integrity, and fiber orientation (SOARES *et al.* 2013). Briefly, this method includes a three-dimensional diffusion model, also referred to as the tensor, which is iteratively estimated for multiple directions. Through the gradient pulse-induced temporal and spatial variations in the magnetic fields, the self-diffusion of water molecules in the tissue can be studied. Albeit also based on Einstein's equation to model diffusion MRI signals, based on the Gaussian principle of water diffusion, analysis MRI diffusion is based on the simpler "apparent diffusion coefficient" principle, emphasizing on non-gaussian diffusion effects, namely the interaction of water diffusion with tissue elements, rendering the model sensitive to physiological and pathological conditions present on the tissue. In several mood disorders, it is proposed that abnormalities in the microstructure of white matter may be the underlying cause of alterations in connectivity, leading to cognitive and emotional symptoms (JENKINS *et al.* 2016; OLVET *et al.* 2016).

Image Acquisition

Functional neuroimaging (Paper I)

Brain scanning session took place after three cycles of SPRM treatment or placebo at the premenstrual phase of the last treatment cycle on a 3.0 Tesla scanner scanner (Achieva dStream, Philips Medical Systems, Best, The Netherlands) ecquipped with a 32-channel head coil. For BOLD fMRI, 240 whole-brain dynamic scans were acquired using a T2*-weighted gradient echo-planar imaging (EPI) sequence with the following parameters: repetition time (TR) = 3000 ms, echo time (TE) = 30 ms, flip angle = 90°, 100 x 97 matrix size, 43 slices, slice thickness= 2.8 mm, acquisition time = 12:11 min. Resulting images have a 1.88 x 1.88 x 2.8 mm3 voxel size.

Structural neuroimaging (Papers II & IV)

Women were scanned twice, once at baseline before treatment administration and a second time at follow-up after three cycles of SPRM or placebo treatment, at the premenstrual phase of the last treatment cycle. A whole-body 3-Tesla scanner scanner (Achieva dStream, Philips Medical Systems, Best, The Netherlands) equipped with a 32-channel head coil was used for the brain scans. 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.

Diffusion tensor neuroimaging (Paper III)

A 3.0 Tesla whole-body scanner (Achieva dStream, Philips Medical Systems, Best, The Netherlands) equipped with a 32-channel head coil was used also for the DTI. DTI data were collected twice, at baseline and at follow-up, using a whole-brain Echo Planar Imaging sequence with the following parameters: repetition time (TR) = 3628 ms, echo time (TE) = 83 ms, field of view (FOV) = 224 mm × 224 mm, data matrix = 128 × 128, voxel size = 1.75 × 1.75 × 2 mm3, slice thickness = 2 mm, flip angle (FA) = 90◦, 48 diffusion-sensitive directions with b = 800 mm2/s, 1 volume with b = 0 mm2/s, and 60 slices without inter-slice gap.

Resting state functional neuroimaging (Paper V)

Resting state data were acquired on the 3.0 Tesla whole-body scanner (Achieva dStream, Philips Medical Systems, Best, The Netherlands) equipped with a 32-channel head coil. A T2*-weighted gradient EPI sequence was used and the following parameters were followed: repetition time (TR) = 2050 ms,

echo time (TE) = 30 ms, flip angle = = 90°, 112 x 112 matrix size, 35 slices, slice thickness= 2.8 mm, acquisition time = 10 min. Resulting images have a 1.88 x 1.88 x 3.5 mm3 voxel size.

fMRI preprocessing and analysis steps (Paper I)

After data collection is complete, both fMRI and MRI data need to undergo a series of preprocessing steps in order to identify and minimize the influence of artifacts that interfere with structure and changes in brain function and validate certain model assumptions. Preprocessing aims to increase signal-to-noise ratio (SNR) by correcting temporal and structural volumes (scans) and transforming the collected data to fulfill the assumptions, by standardizing the brain regions location across subjects (HUETTEL *et al.* 2004). The first images of brain slices are usually discarded, as the longitudinal magnetization would not yet have the time to stabilize and reach equilibrium, which leads to the appearance of a large signal. The raw data from the scans need to be consistent and similar to one another to proceed with the statistical analysis. A visual quality control is the first approach to reveal gross errors such as excessive motion, anatomic anomalies, missing slices, and other artifacts that could tamper with the quality of the analysis.

Motion and time correction are next, known as realignment. As the data acquisition occurs simultaneously through pulse sequences, the slice selection is done by using radiofrequency excitation (SLADKY *et al.* 2011). Data acquisition using eco- planar imaging (T2*) takes time to occur and slices within a time sequence have different acquisition times. In most procedures, collecting data from the entire brain, a typical pulse sequence acquires several slices throughout the TR, using either ascending/ descending or interleaved slice acquisition is used within each volume; in the former, the slices are collected consecutively and in the latter, which is mostly used nowadays, the scanner first collects the odd-numbered slices and then the even- numbered ones to avoid cross- slice excitation (HUETTEL *et al.* 2004). In both slice collection types, there is the possibility of BOLD signal being sampled at different parts of the brain being sampled in different time-points within the TR and BOLD response in voxels for later slices would appear ahead of that of earlier slices, which would confer problems in the analysis, if uncorrected. Such issue is eliminated using temporal interpolation, a process that brings all the slices to the same time-point reference (POWER *et al.* 2017).

Once that is done, movement correction takes place, original raw data is resampled to obtain the values that would have been obtained, provided that no head movement occurred (rigid- body registration). This process is called spatial interpolation, a similar process to the temporal one, but considering three dimensions of space. The data gathered should be correlated to the experimental task performed and since the fMRI scanner is highly sensitive even

to slight body motion, slices need to be realigned, or else one might lose valuable data (GROOTOONK *et al.* 2000). In motion correction, all 3D images are registered and resampled to a selected reference image, for example the first image, to be in the same orientation as the reference image. In this process, when a volume is not in line with the others, rigid- body transformations and intra- modal voxel similarity functions are performed to model the changes between images and statistically compare it to the reference volume. Once those steps are completed and each voxel's data from a brain region is sampled at regular intervals throughout time series, images need to be resliced before analysis.

The realignment steps are sufficient to proceed with the analysis of the functional data, but in most cases, the registrations are performed quite rapidly, leading to low- resolution and limited anatomical contrast. Thus two additional procedures are typically added in fMRI studies, especially those that used voxel- based analyses (HUETTEL *et al.* 2004). They are usually co-registered to onto high- resolution and high- contrast structural images from the same subjects. Comparing data inter-individual activation is challenging, as physiological characteristics (size of different participants' brains, variation in shape, etc.) can vary across individuals. To resolve this, images go through the normalization process, where all the subjects' data should be transformed into same size and shape as a reference brain, created from a representative set of individual brains. Normalization rescales the mean intensity of the fMRI signal in order to compensate for variations of global signal both within sessions and between sessions. Images are normalized to a standard space, rendering the results from different studies comparable. Reporting data as coordinates within a common normalization scheme is encouraged and thus two basic stereotaxic spaces are commonly used in reported fMRI data, the Talairach space and the Montreal Neurological Institute (MNI) space (POLDRACK *et al.* 2008). Spatial normalization is achieved by using a 12-parameter affine registration that includes 3 translations, 3 rotations 3 zooms and 3 shears and fits the overall size and shapes and compensates for major head shape and position. After that, the registration should be refined, using non-linear deformations. Normalization of the time-series offer two main options; the structural normalization and the EPI normalization (CALHOUN *et al.* 2017). Structural MRI data are registered based on the T1 image, to the mean of the functional MRI, using a T1 template, while the EPI normalization, following a similar procedure, in which EPI images are normalized to an EPI template. The results are then overwritten, to the fMRI time- series.

The final step of preprocessing is the spatial filtering, or smoothing, a useful for in- depth analysis and minimizing of irrelevant signal variation, recognized as noise that interferes with BOLD signal, smoothing residual differences across individuals, along with the possibility of using filters to minimize physiological noise (HUETTEL *et al.* 2004). Spatial smoothing is implemented by using, again, a Gaussian filter and convolution, contributing to the increase

of SNR in the data which render the data more normally distributed and more suitable for parametric tests. Furthermore, using random field theory when correcting the results, increases the statistical validity and generalizability to the population (NICHOLS 2012).

Here, functional MR data were pre-processed and analyzed using Statistical Parametric Mapping (SPM12, Welcome Centre for Human Neuroimaging, University College London, London UK). The images were slice-timing corrected, spatially aligned, and unwarped. The structural image was co-registered to the first functional image and then normalized into canonical MNI space. The resulting deformation field was then applied to the functional images. We then proceeded to the first-level analysis where the change in BOLD signal was modelled for the task conditions for each subject.

Voxel-based morphometry (Papers II & IV)

Grey matter is the CNS component containing the neuronal cell bodies. As a measure, grey matter volume is one of the components researchers assess macroscopic brain morphology patterns. To this end, different neuroanatomical techniques have been developed to obtain such structural information from MRI images. Voxel-based morphometry (VBM) is a sensitive tool that allows for voxel-wise estimation of local tissue alterations. The technique is used to estimate and compare grey matter (and/or white matter) densities, namely the probability of a specific voxel to be classified as a specific type of tissue (ASHBURNER AND FRISTON 2000) and it is particularly sensitive in studying small-scale structural alterations. The standard VBM procedure (Figure 6), available in software such as the Statistical Parametric Mapping software offers a pipeline of normalizing, segmenting, and smoothing the structural images using statistical parametric mapping to infer local tissue ratio.

The first step of segmentation aims to distinguish the different tissues (white matter, grey matter, and cerebrospinal fluid (CSF)). Due to the similarity of white and grey matter intensities, a robust contrast, such as the optimized rapid gradient-echo (MP-RAGE) sequence (MUGLER III AND BROOKEMAN 1990) is required to assure the accuracy of the segmentation process. The segmentation step is a unified probabilistic procedure during which the images undergo registration, segmentation, and bias correction within the same model (ASHBURNER AND FRISTON 2000). Once the process is complete, tissue classification fitting of the six different components and tissue types (grey matter, white matter, CSF, bone, soft tissue, and air) is performed through a six-component Gaussian mixture model (ASHBURNER AND FRISTON 2005). Subsequent spatial normalization takes place, to ensure data comparability, which transforms the images into stereotactic space using linear and non-linear components through a 12-parameter affine transformation to a common template. Following the segmentation and normalization steps, the spatial smoothing

procedure takes place, which applies a low-pass Gaussian kernel that "blurs" the normalized tissue segments to compensate precisely for the effects of spatial normalization. The Gaussian kernel is essential for accounting for the multiple comparisons problem and is based on the random fields theory. An isotopic Gaussian kernel of a full width at half maximum (FWHM), customarily at around 8 - 12mm for VBM studies, is used to spatially smooth the images. The smoothing procedure offers a voxel by voxel estimation of an average grey and white matter ratio, allowing for the comparison in approaches such as the regions of interest (ASHBURNER AND FRISTON 2000). After the completion of these steps and upon homogeneity check procedures, the general linear model (GLM) can be used for statistical analysis offering information on grey matter volume changes or grey matter relationships with different variables, offering a robust estimation of whole-brain or regional volumetric patterns.

For the structural MR data in paper II, two preprocessing modules were employed. For the grey matter analyses, the SPM12 software was used to normalize the images to standard MNI space, correct for intensity variation, and segment them into the different tissues, namely grey and white matter, CSF, bone, soft tissue, and background (ASHBURNER AND FRISTON 2000). Then, the images were spatially normalized on volumetric data and underwent quality assessment. Subcortical segmentation was done separately with the accurate automatic segmentation pipeline on FSL-FIRST.

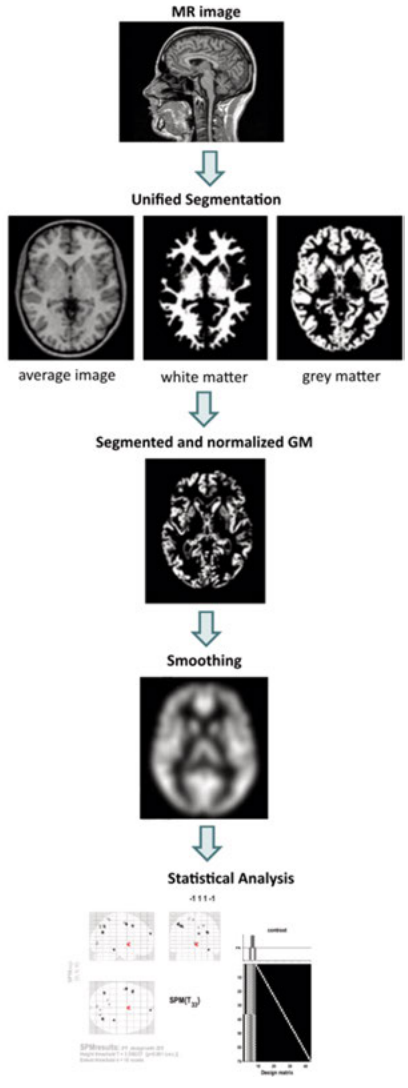

Figure 6. VBM preprocessing and analysis framework using CAT12 toolbox and SPM12 software summarized.

Surface-based morphometry (Paper II)

The complex system of convoluted gyri and sulci of the cortical surface offer further comprehensive characterization of the macroscopic elements in brain anatomy. Grey matter volume represents cortical thickness and surface (WINKLER *et al.* 2010). Cortical thickness is a measure relevant to the number of cortical neurons in the radial cortical columns, which are reflected in the surface area (RAKIC 2009). Gyrification, sulcal depth, and fractal dimension

are associated with radial neuronal migration due to the tension caused by neuronal connections (WHITE *et al.* 2010). Volumetric changes across the brain surface are not uniform, therefore combining additional features of cortical morphology is informative in accurately characterizing localized structural differences and relationships.

The surface-based morphometry (SBM) automated pipeline provided by the CAT12 toolbox, run on SPM12, includes a precision segmentation module offering the opportunity to discriminate volume into its different parameters, cortical thickness and surface area. With the automated pipeline it is possible to preprocess several subjects at once, following the steps of surface extraction, vertex-wise parameter calculation, and cortical surface reconstruction in order to quantify the different morphological parameters of brain anatomy (LUDERS *et al.* 2006; DAHNKE *et al.* 2013).

Tract-based spatial statistics (Paper III)

Tract based statistics (TBSS) is a rather recent voxel-wise whole-brain data analysis approach of DTI data applying non-linear registration to circumvent alignment issues that emerge from the low-resolution nature of DTI data. This is done by initially and co-registering the FA images to each other and then calculate the diffusion tensor, the tensor eigenvalues and finally the FA (SMITH *et al.* 2006). Individual FA images are first affine-transformed and nonlinearly warped (registered) to each other and the algorithm is using intermediate degrees of freedom in order to preserve the individual tract topology (SMITH *et al.* 2006). Finally, each FA imaged is averaged to a mean FA image which represents the common to all subject's tracts. Mean FA provides the values for the group skeleton, namely by "feeding" the highest FA values from the nearest tract center to the group FA skeleton (SMITH *et al.* 2006).

Hormonal analysis (All studies)

Venous blood samples were collected from each participant at the beginning of every session to determine the levels of oestradiol, progesterone, testosterone, and cortisol. Steroid hormones were measured in serum at the Core Facility of Metabolomics at the University of Bergen by liquid chromatography – tandem mass spectrometry. Sample processing was robotized (Hamilton STAR) and included protein precipitation with acetonitrile and liquid–liquid extraction with ethylacetate–heptane. The samples were analyzed on a Waters Acquity UPLC system connected to a Waters Xevo TQ-S tandem mass spectrometer. The compounds were separated on a C-18 column (50 x 2.1 mm, 1.7 mm particle size), which is developed by gradient elution over 14 min, using water and methanol containing ammonium hydroxide as mobile phases.

They were detected in negative (e.g. oestradiol) or positive ion (progesterone and testosterone) MRM mode. Two product ions are monitored for each compound to check for interferences. The method is highly selective and separates several isomers, e.g. epitestosterone and testosterone. The method is validated for oestradiol [sensitivity 3.6 pmol/L (LLQ) and 1.2 pmol/L (LOD) and total control volume (CV) for intermediate concentrations 5.0 %], progesterone (10.3%), testosterone (3.2%), and cortisol (1.9%). Conjugated and non-conjugated steroids were analyzed in separate runs with slightly different gradients.

Analysis of serum sex hormone-binding globulin (SHBG) and albumin was measured with immunometric electrochemiluminescense at the accredited laboratory of Department of Clinical Chemistry, Uppsala University Hospital. The Vermeulen method was used to estimate serum concentrations of bioavailable testosterone by use of the Mazer spreadsheet (MAZER 2009), and calculations included SHBG, albumin and testosterone levels. The free androgen index (FAI) and free oestrogen index (FEI) were calculated as the ratio of total testosterone and oestradiol to SHBG values.

PSAP (Study I)

All participants were asked to have their brain scanned while performing the Point Subtraction Aggression Paradigm (PSAP) (GENIOLE *et al.* 2017) (Figure 7) during the late luteal phase of the menstrual cycle. The paradigm is based on a computer-simulated social interaction in which participants played against a fictitious other person. Prior to scanning, the participants received oral instructions about the paradigm. They were told that they would play a game where the goal is to score as many points as possible, which could be exchanged for money. During the PSAP, participants had to press one of three buttons (Option 1, 2 and 3) a given number of times in order to achieve a particular outcome. Thus, pressing 100 consecutive times the button for Option 1 resulted in the participant earning 1 point, pressing 10 consecutive times the button for Option 2 resulted in the virtual opponent having a point taken away (aggressive behaviour), and pressing 10 consecutive times the button for Option 3 briefly protected the participant from having points stolen (Fig 1A). Participants responded via a five-finger button-box (Celeritas®, Fiber Optic Response System, Psychology Software Tools, Pittsburgh, PA) on the right hand and had to complete a started option before choosing a new one. Options 1, 2 and 3 corresponded to the index, middle and ring finger keys, respectively. The status of the game, including total score, presses and options were projected onto a screen viewed by the participant while lying in the scanner (Fig. 1B). When the press counter reached 100, participants were informed about earning a point through black flashing positive symbols ("+") and the subsequent total score increased by one point (Fig. 1C). Similarly, red flashing negative symbols ("-") indicated when points were stolen from the participant,

and the total score was decreased by one point (Fig. 1D). If participants were not using Option 2 or Option 3 during the task, they were provoked by having points stolen every 6-60 s. Provocations occurred immediately if participants did not use Option 2 or 3 for 5 min. Completing Option 2 or 3 initiated a provocation-free interval of maximum 60 s. Nonetheless, participants were only aware of the protective effect of Option 3. Participants were informed that they could not keep the points stolen from the opponent while the opponent was allowed to keep the points stolen from the participant. Thus, Option 2 represents aggressive behaviour without direct monetary reward. Behavioral output variables were: the total number of points won during the task, the total number of provocations received and the number of Option 1, Option 2 and Option 3 presses. In addition, a "PSAP aggressive behaviour" metric was defined as [1000 × No. Option 2]/[No. of total button presses × No. of provocations], as previously described . While in the scanner, participants completed a one-minute trial session immediately before playing one 12-minute session of the PSAP, as described in (DA CUNHA-BANG *et al.* 2018). The paradigm was programmed using E-prime® v2.0 (Psychological Software Tools, Pittsburgh, PA).

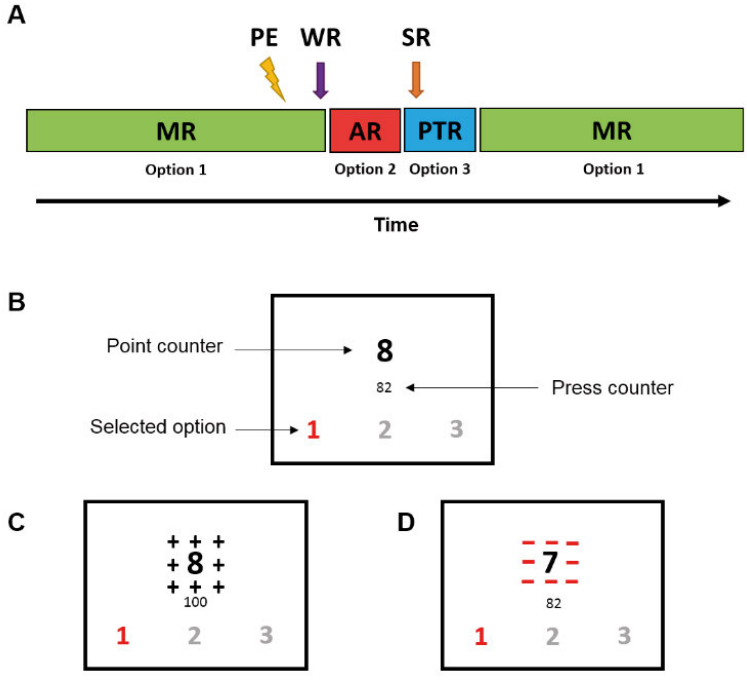

Figure 7. (A) The bar represents the conditions and events illustrated either as blocks or arrows: MR: Monetary Response, AR: Aggressive Response, PTR: Protective Response. The ligthning icon (PE) represents the provocation event, the purple arrow (WR) the Winning Reward and the orange arrow (SR) the stealing reward. [7]. (B) Illustrative examples of what seen by the participant on the screen. (C) End of monetary response block, indicating points earned. (D) Provocation screen, indicating point stolen with flashing red icons, and the remaining points.

Statistics

General Linear Model (Papers I, II, IV, & V)

Once the preprocessing steps are complete, the images are ready to be analyzed. Currently, the widely used method for MRI and especially fMRI data analysis is multiple regression, which is based on hypothesis-driven models of expected brain activation, in order to match multiple regressors (distinct predictions) with different hypothesized processes (HUETTEL *et al.* 2004). The statistical analysis measures the regressors' correspondence to the acquired voxel data and can thus distinguish between input driven hemodynamic response and residual noise, using the GLM. Massive univariate approach, in

which the term 'univariate' refers to the single response variable, uses GLM which assumes a linear combination of the different explanatory variables and the response variable, which is the observed experimental data, with a "well-behaved" error term; since this is a hypothesis driver analysis that requires correction and comparison of multiple voxels, a null and alternative hypotheses should be posed, to express the expected outcome in the latter and aiming to disprove the former. The model is used in comparisons with a plethora of voxels (more than 10000) and to avoid committing type I errors (determining inactive voxels as active), one needs to set a significance threshold, to minimize the chance factor. If the threshold is set at $\alpha = 0.05$, which is usually applied in the social sciences, that would include about 6000 or more voxels, increasing the possibility of a false positive; accordingly, at $\alpha = 0.01$, more than 1000 etc. Therefore, to minimize the false positive results, Bonferroni correction is applied, which decreases Type I error, increasing, however, the Type II error probability, which ignores the true activation and can be solved using the Gaussian random field theory to accurately estimate the number of statistical test (HUETTEL *et al.* 2004).

With regards to functional neuroimaging, the general lineal model (GLM) (CHRISTENSEN 2002) is widely used in modelling the BOLD response, by fitting each brain voxel separately using ordinary least squares (OLS) to a mass univariate model (STEPHAN 2014). In general, the GLM framework aims to answer on the magnitude and variance of the effect of a number of variables on a response variable. In order to answer what is the contribution of each task-related predictor in explaining the signal variability, the time course of the BOLD signal is modeled for each voxel as the weighted sum of the predictor variables, which correspond to the experimental design (onset, offset, duration of conditions) and an error term (ε) (HUETTEL *et al.* 2004). The BOLD signal intensity, therefore, for each observation (y) would be a product of the sum of the predictors ($x_{i1} \ldots x_{ip}$) scaled by a parameter (β): $y_i \alpha + x_{i1} \beta_{i1} + x_{i2} \beta_{i2} \ldots + x_{ip} \beta_{ip} \varepsilon$. This is otherwise known as first-level analysis, where the BOLD intensity estimation is done for each subject separately.

Psychophysiological Interaction analysis (Paper I)

Psychophysiological Interaction (PPI) analysis explores the relationship between brain regions in terms of certain experimental manipulations and thus a specific cognitive or emotional state. It is based on two principles, namely functional integration, which is defined as the interactions between specialized areas or neuronal populations and their dependency on cognitive context (FRISTON *et al.* 1997), and functional connectivity, which corresponds to the temporal correlation between the signal time series of different brain regions (STEPHAN *et al.* 2009). The psychological part of the analysis description refers to the experimental variable's time course values and the physiological part refers to the BOLD time course at a selected ROI. It is a GLM based

method, where the regression can be understood in terms of the contribution of a seed region (a.k.a. reference region) to one or several regions in question (FRISTON *et al.* 1997).

In paper I we used PPI analysis to assess the interactive effects of the condition-specific BOLD response within the dACC/dmPFC with other regions. To this end, single-subject matrices, like the ones used to investigate the main task effects, were estimated using the fronto-cingulate cluster as a seed region, from which the BOLD signal time series was extracted using the volume of interest time series, serving as the physiological regressor in the analysis. The aggressive response condition contrast (AR> MR) was used as the psychological regressor. The individual contrast images were used to assess group differences in the contribution of the ACC and left mPFC in the activation of other brain regions through two-sample t-tests.

Permutation and randomization tests (Papers I & III)

Permutation tests are part of non-parametric methods that are used for GLM in the field of neuroimaging to determine voxel- or cluster- wise significance while addressing the multiple comparisons problem (WINKLER *et al.* 2014). For paper I, the Statistical non-Parametric Mapping (SnPM) 13.1.06 toolbox was used to exclude the possibility of false positives from the parametric tests on treatment group differences regarding BOLD reactivity. Similar to the parametric testing, the GLM is used to produce *t*-statistic images and permutation inference is used to assess the significance of the comparisons of the chosen set of imaging by relabeling and computing the data distribution without any initial assumptions other than the initial randomization of the data. In paper I, a two-groups – two-sample *t*-test was used and the number of permutations was set to the default 5000, a higher number than the commonly suggested 1000 that has proven to be sufficient in characterizing the permutation distribution (WINKLER *et al.* 2014). For paper III, the fsl tool "randomise" (WINKLER *et al.* 2014) was used for non-parametric voxel-wise permutation analyses and the amount of permutations was also set to 5000.

Two-way ANOVA (Paper I)

Typically, two-way analysis of variance (ANOVA) is used to assess the differences between the means of two groups. In paper I, two-way ANOVAs were used to explore the relationship between the ROI BOLD reactivity and task behavior, symptom severity, psychometric scores, and hormonal levels. One model was defined for each variable of interest on SPM12 (SPM12, Wellcome Centre for Human Neuroimaging, University College London, London UK), with each variable (task behavior, symptom severity, psychometric scores, and hormonal levels) set as within subject factor and the treatment group (SPRM vs. placebo) as the between group factor.

Mann-Whitney U tests (Papers II, IV & V)

The Mann-Whitney U test is a non-parametric test used in assessing differences between two samples. The basic assumptions of the tests are that the samples are independent, the distributions are equal under the null hypothesis and unequal under the alternative hypothesis. Since non-parametric methods do not entail any assumptions about the underlying distribution, in papers I and II, the test was used to assess treatment group comparisons with regards to symptom severity (papers I and II), task behavior (paper I), and hormonal levels (paper I) when the data were not normally distributed.

Pearson Partial Correlation test (Paper I)

Parametric Pearson partial correlation tests were used to investigate the relationship between and task behavior, symptom severity, psychometric scores, hormonal levels, and the BOLD response in the aggressive response condition for each treatment group separately. Partial correlations are appropriate when the control for a confounding variable is needed and in this paper the number of received provocations during the task and the number of the total button presses were controlled for, as they are both numerically related with the variables of interest.

Seed-based connectivity analyses (Paper V)

Seed-based connectivity analyses aim to characterize connectivity patterns between a seed region, namely an apriori selected ROI and either another ROI or all the other voxels in the brain (WHITFIELD-GABRIELI AND NIETO-CASTANON 2012). To this end, seed-based connectivity maps (SBC) are computed, as the Fisher-transformed bivariate correlation coefficients from a GLM, fitted for each pair of seeds and target regions/areas to assess the relationship between the BOLD timeseries in a ROI and each voxel's timeseries. SBC maps are condition-specific (in this case only the rest condition). Each participant's scan is boxcar signal weighted to characterize the condition (rest) and convolved with the canonical hemodynamic response function.

Spearman rank-order correlation test (Papers II & V)

The Spearman rank-order correlation coefficient is the non-parametric test for assessing the association between two ranked variables. This method was used in paper II to assess the direction and strength of the relationship between the change in grey matter and the change in symptom severity. Additionally, spearman rho correlation analyses were computed in paper V to investigate the relationship between change in rs-FC and change in symptom severity and hormonal levels from baseline.

Family-wise error correction for multiple comparisons (Papers I, II, III, & IV)

The family-wise error (FWE) approach is a method to account for the multiple comparisons problem that inflates the false positive findings incidence. The FWE correction calculates the probability of one or more "families" of multiple tests to be false (HSUEH *et al.* 2003). For papers II, II, and IV FWE corrections were implemented across voxels.

In paper I, the cluster-extent correction was used to account for the FWE rate when investigating the treatment effect on BOLD reactivity within the ROIs, Specifically, an initial lenient $p = 0.001$ uncorrected voxel-wise threshold was used, combined with a $p = 0.05$ cluster extent FWE corrected threshold that differed for each ROI: $k \geq 111$ for PFC; $k \geq 28$ for ACC; $k \geq 22$ for the insulae; $k \geq 25$ for the striatum; and $k \geq 1$ for the amygdalae.

False positive discovery rate correction for multiple comparisons (Papers II & V)

In paper II, the false discovery rate (FDR) method was used to control for multiple comparisons. The FDR measurement represents the number of the falsely rejected null hypotheses among the significant findings (CHONG *et al.* 2015). Specifically, the Benjamin and Hochberg method was used here, which constitutes a step-up procedure that initially orders the p-values from the smallest to the largest for all tests and subsequently calculates a critical value for each p-value, and then compares the original p-values with the critical values. In our papers II and V, we applied the FDR correction for the number of tests for all analyses, using a lenient $q < 0.1$ threshold due to the novelty of the study.

GLM repeated-measures ANOVA (All papers)

In order to assess the treatment effect on grey matter volume and cortical surface metrics, the GLM repeated measures ANOVA was used for each one of the ROIs, with time (baseline, follow-up) as the within-subjects factor and treatment group (SPRM, placebo) as the between-subjects factor.

Threshold-free cluster enhancement methodology (Papers II, III, & IV)

In papers II, III, and IV the treatment effect on brain metrics (GMV, FA, MD, RD, AD, WMV) was assessed through non-parametric mixed measures ANOVA to compute the time (baseline vs. follow-up sessions) by treatment (SPRM vs. placebo) interaction effect. To this end, the threshold free cluster enhancement (TFCE) approach was used, a novel method in finding

significant clusters without using arbitrary cluster forming thresholds (SMITH AND NICHOLS 2009). Shortly, the TFCE algorithm is enhancing the difference in cluster-like regions in comparison to background regions, that are considered as noise, resulting in improved discrimination between noise and spatially-related densities. The TFCE thresholded results (images) were then transformed to voxel-wise p-values through permutation testing. The number of permutations was set to 5000.

Results and Discussion

All studies

Thirty women, aged between 22-44 were included in the fMRI analysis (paper I), from which fifteen were randomized to SPRM and fifteen to placebo treatments. Women did not differ in symptom severity, psychometric scores, or hormonal levels before randomization (at baseline). Symptom severity was significantly lower for women receiving SPRM treatment according to the total summed DRSP score and all DRSP subscales, apart from the irritability subscale, which was marginally significant. Women in the SPRM group showed significantly lower state aggression. Besides progesterone, which was pharmacologically manipulated, there was no difference in hormonal levels between treatment groups.

For the structural neuroimaging study, thirty-five women's data were analyzed, from which 18 received SPRM treatment and 17 received placebo. The mean age was 34 at baseline and 35 at follow-up for the SPRM group and 35 at baseline and 36 at follow-up for the placebo group. No baseline differences were found in symptom severity and the treatment groups significantly differed with regards to the total DRSP score, the anxiety and affective lability subscales scores at follow-up. Similar sample characteristics were present in the other Papers, though one or two individuals may have not been included due to technical issues (Papers II and IV), motion artifacts (Papers I and III).

Study I

Women with PMDD, after three cycles of treatment with SPRM or placebo, have been performing the PSAP test while having their brain scanned using fMRI. Three-month low dose SPRM treatment was associated with greater BOLD signal in the aggressive response following provocation compared to placebo in a bilateral cluster extending over both the dACC and dmPFC (Figure 8). Moreover, regarding task behaviour, significant treatment-by-aggressive responses (button presses) interaction effects on dACC/ dmPFC were noted, driven by a negative correlation between the fronto-cingulate BOLD reactivity and aggressive responses in the placebo group. Previous neuroimaging evidence has indicated fronto-cortical regions as differentially activated during emotion processing between women with PMDD and controls, namely

blunted activation of the pregenual ACC and ventromedial PFC while discriminating facial emotional expression stimuli (COMASCO *et al.* 2014). The present findings pinpoint for the first time the importance of the dorsal parts of ACC and PFC in PMDD, specifically increased activation in the women treated with SPRM was interpreted as a beneficial effect of the pharmacological therapy in enhancing functioning of top-down regulatory regions. Both regions subserve cognitive control and emotion regulation (ETKIN *et al.* 2011).

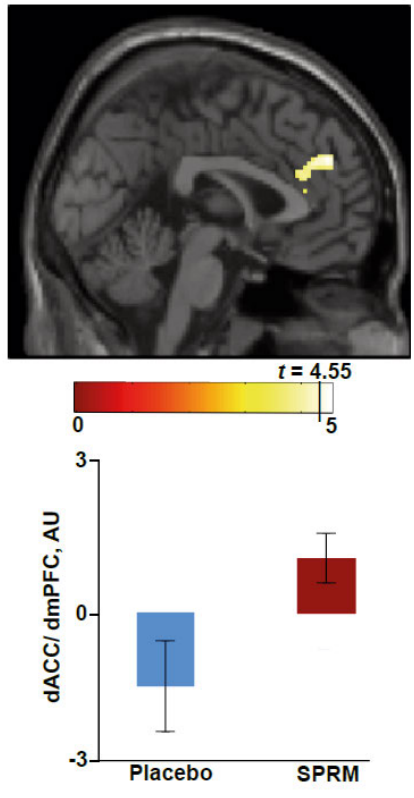

Figure 8. Enhanced BOLD reactivity (SE: 95% CI) after treatment with SPRM was seen in women with PMDD (n = 15) in the contrast aggressive response > monetary response, when compared to the placebo (n = 15) within the combined dACC/ dmPFC ROI mask (three maxima: [x, y, z: 0, 46, 30, −8, 46, 20, and 4, 34, 20]; k = 199; T = 4.55; pFWE-cluster = 1.76E-05). The first maximum is illustrated in the graph. The signal mean time-course was extracted for treatment group differences in BOLD response visualization.

Anatomically, the regions within which we observed the treatment effect are part of the dorsal top-down control system (i.e., Broamann Areas 9 and 24/32). Both regions are part of frontal attentional and control networks and shown to be affected by hormonal fluctuations of the menstrual cycle phase and oral contraceptive treatment (DUBOL *et al.* 2020; REHBEIN *et al.* 2021). The medial

part of the superior frontal gyrus constitutes part of the medial PFC, modulated by ovarian hormone fluctuations and central to mood disorders (VAN WINGEN *et al.* 2011). The dorsolateral and medial PFC show heightened reactivity during the luteal phase in PMDD patients during anticipation, but not exposure, to negative emotional stimuli (GINGNELL *et al.* 2013). Regarding the ACC, besides its role in higher regulatory processing through sympathetic autonomic arousal in demanding contexts, increasing evidence renders the ACC central in negative affect experience, adjusting cognitive control to subjective evaluations (SPUNT *et al.* 2012). Being part of the salience attentional network, it constitutes a significant ROI in mood disorders (DREVETS 1999), with especially dorsal reactivity being one of the key regions in negative affect in major depressive disorder (HAMILTON *et al.* 2012).

Behaviour-wise, the women under SPRM treatment did not choose the protective response button as often as the placebo group, otherwise there was no other significant difference with regards to task performance. However, fronto-cingulate reactivity was influenced by the relationship between aggressive responses and treatment group, described as a negative correlation between aggressive responses and BOLD reactivity in the placebo group at a trend level. This may imply better control of the SPRM group over their aggression. However, no certain conclusions can be drawn as no such relationship was confirmed by the statistical analyses, likely due to limited statistical power.

Altogether, the results of this pharmaco-neuroimaging study on PMDD point to enhanced cognitive control during reactive aggression being associated with SPRM treatment. Potentially, stable levels of progesterone and oestrogen are beneficial while processing provocations and reacting aggressively.

Study II

We examined whether three cycles of SPRM treatment compared to placebo would influence grey matter volume or cortical surface in women with PMDD. Despite the positive effect of SPRM treatment on PMDD symptoms (COMASCO *et al.* 2021), and the enhancing effect on aggression-related fronto-cingulate activation (KALTSOUNI *et al.* 2021), the treatment did not impact brain structure. This was observed both when we explored treatment effects on grey matter and cortical surface at a whole-brain level due to the novelty of the study, and when we employed a priory hypothesis based on the regions suggested to be implicated in the neural circuit underlying PMDD (DUBOL *et al.* 2020).

Early lesion studies provide evidence on progesterone's neuroprotective and neuroplastic effects on different types of neurons in regions such as the cerebellum and hippocampus (GONZÁLEZ-VIDAL *et al.* 1998; XU *et al.* 2001). However, these are effects that cannot be assessed through structural MRI.

Structural MRI, and especially when applying high accuracy methods such as VBM, is a useful tool in tracing *in vivo* structural alterations of brain anatomy (ASHBURNER AND FRISTON 2000). It has been proven useful in characterizing neurotoxic effects, lesions, and brain volume loss in different disorders, but it is still a composite measure of neuronal tissue (RIDGWAY *et al.* 2008).

Another important point is that the nature of PMDD symptomatology is cyclic, and it is reasonable to assume changes in mood are underlined by functional events rather than long-term macrostructural changes, such as neuronal loss or atrophy. It is possible that the positive effect of SPRM treatment on PMDD negative affect is either not mediated by structural alterations or longer treatment regimens are needed to observe such changes. Although sparse and inconsistent, with profound methodological discrepancies between study designs, literature provides some evidence on the anatomical signatures of PMDD (DUBOL *et al.* 2020). Indeed, the sole significant finding on GMV differences between PMDD sufferers and healthy controls is located in the cerebellum, but shown to be age-related, as the observed group difference was significant for older women (BERMAN *et al.* 2013). According to the authors, age-related grey matter changes could characterize PMDD. This assumption finds support in evidence showing that symptom can increase with age (SYLVÉN *et al.* 2013) and potentially older women find it more difficult to cope with the premenstrual negative affect. The duration of premenstrual suffering spans decades across the reproductive years of those affected(RAPKIN AND WINER 2009) and it is thus probable that a three-month treatment duration was not enough to observe effects on grey matter. In our sample, the mean age of women was around thirty years (paper I: 35 ± 8 years old; paper II: 34.4 ± 5 years old) and age was considered as covariate. In the current study, changes might have also occurred on the synaptic transmission level and, as we observed some trend relationships between structural alterations and changes in symptoms (likely driven by the SPRM group), any structural correlates might need longer regimens to be traceable, as they might result from long-term neuroadaptive processes, as opposed to psychotropic treatments (ZHONG AND YAN 2004).

However, recent data-driven classification findings could distinguish PMDD sufferers from healthy controls in terms of GMV with 74% accuracy (DUBOL *et al.* 2022a). Such differences were found in the cerebellum and ventral posterior cortices (KALTSOUNI *et al.* 2022), as well as subcortical regions, while another research study revealed relationships between GMV and surface measures with both affective and physical symptoms in the PMDD sample (DUBOL *et al.* 2022b). It cannot, therefore, be ruled out that while GMV alterations are part of PMDD pathophysiology, they do not constitute part of SPRM treatment's mechanism for symptom relief.

Study III

In order to characterize white matter microstructure after treatment with SPRM or a placebo we utilized DTI using the FA, MD, RD, and AD metrics to define white matter integrity. No longitudinal differences between groups were found (Figure 9). Additionally, there was no correlation observed between symptom improvement and changes in white matter microstructure over time. However, in secondary cross-sectional comparisons at follow-up, the SPRM group exhibited lower FA and higher MD, RD, and AD in widespread white matter projection, association, as well as commissural tracts connecting cortical or cortical with subcortical structures (Figures 10, 11, 12, 13). Such structures included the anterior and/or superior corona radiata, anterior thalamic radiation, fornix, fronto-occipital fasciculi, superior longitudinal fasciculi, uncinate fasciculi, corpus callosum, and cerebral peduncle. Effect sizes for the aforementioned effects ranged between $d = 0.41 – 0.64$.

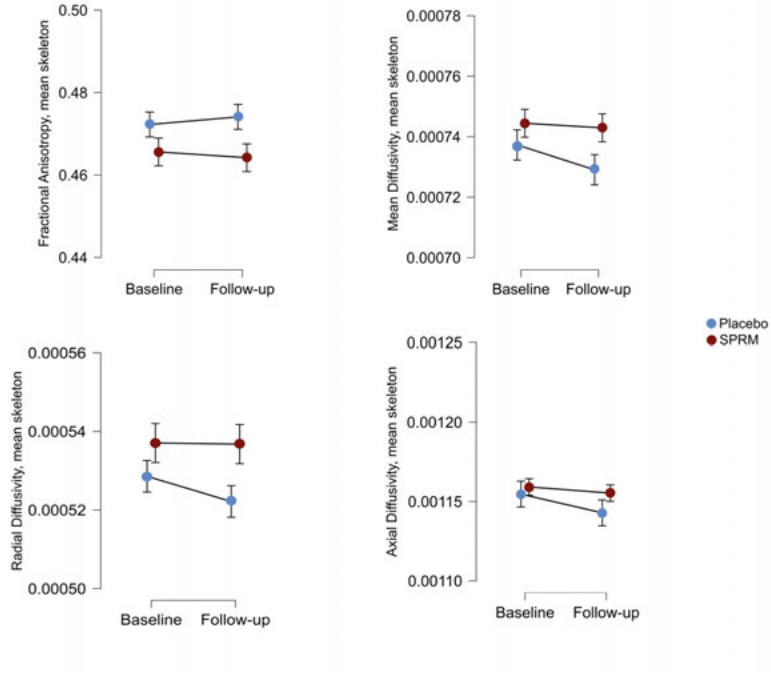

Figure 9. Whole-brain voxel-wise tract-based spatial statistics showed no longitudinal effects between treatment groups on FA, MD, RD, and AD. Mean values over the whole-brain skeleton for DTI metrics were extracted for illustration purposes.

This is the first study striving to characterize the white matter integrity of individuals with PMDD following hormonal manipulation. While caution is warranted in directly attributing diffusivity patterns to neurobiological processes, the conjunction of lower FA along with heightened MD, RD, and AD

has been linked to myelin and axonal degeneration (SEN AND BASSER 2005). In particular, diminished FA is thought to correspond to less coherent white matter tracts (SOARES *et al.* 2013) and in combination with increase in another diffusivity metric, it could imply myelin loss (SUN *et al.* 2006) or axonal damage (CONCHA *et al.* 2006). Considering this, it is possible that three-month treatment with SPRM prompted inflammatory brain response, despite the previously documented improvement in mood symptoms (COMASCO *et al.* 2021). Such assumption is further corroborated by the lack of correlation between change in white matter integrity and symptom severity.

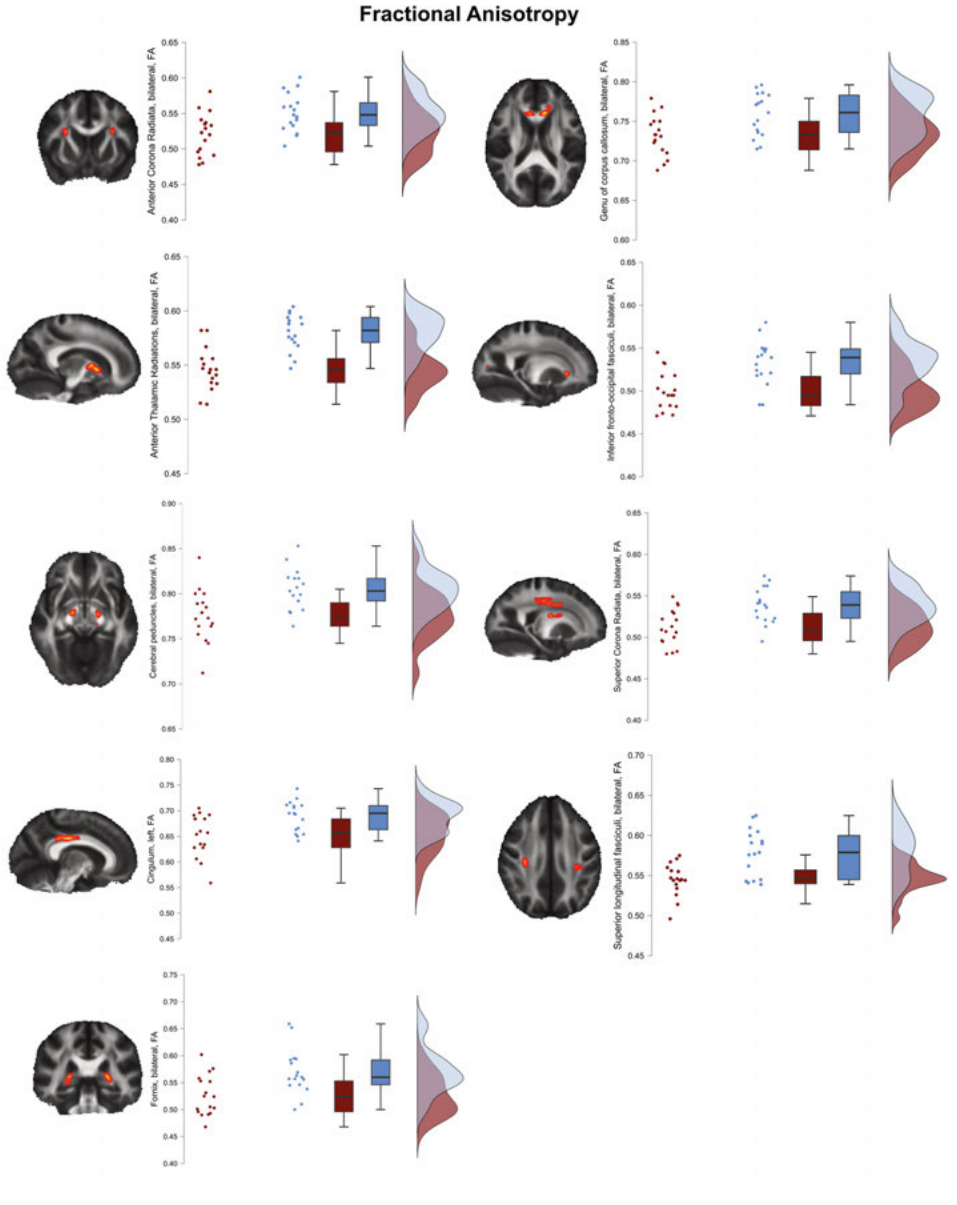

Figure 10. Whole-brain voxel-wise tract-based spatial statistics revealed SPRM and placebo treatment group cross-sectional differences at follow-up for fractional anisotropy anisotropy in the bilateral anterior corona radiata, anterior thalamic radiations, cerebral peduncles, fornix, genu of corpus callosum, inferior fronto-occipital fasciculi, superior longitudinal fasciculi, superior corona radiata, and the left cingulum.

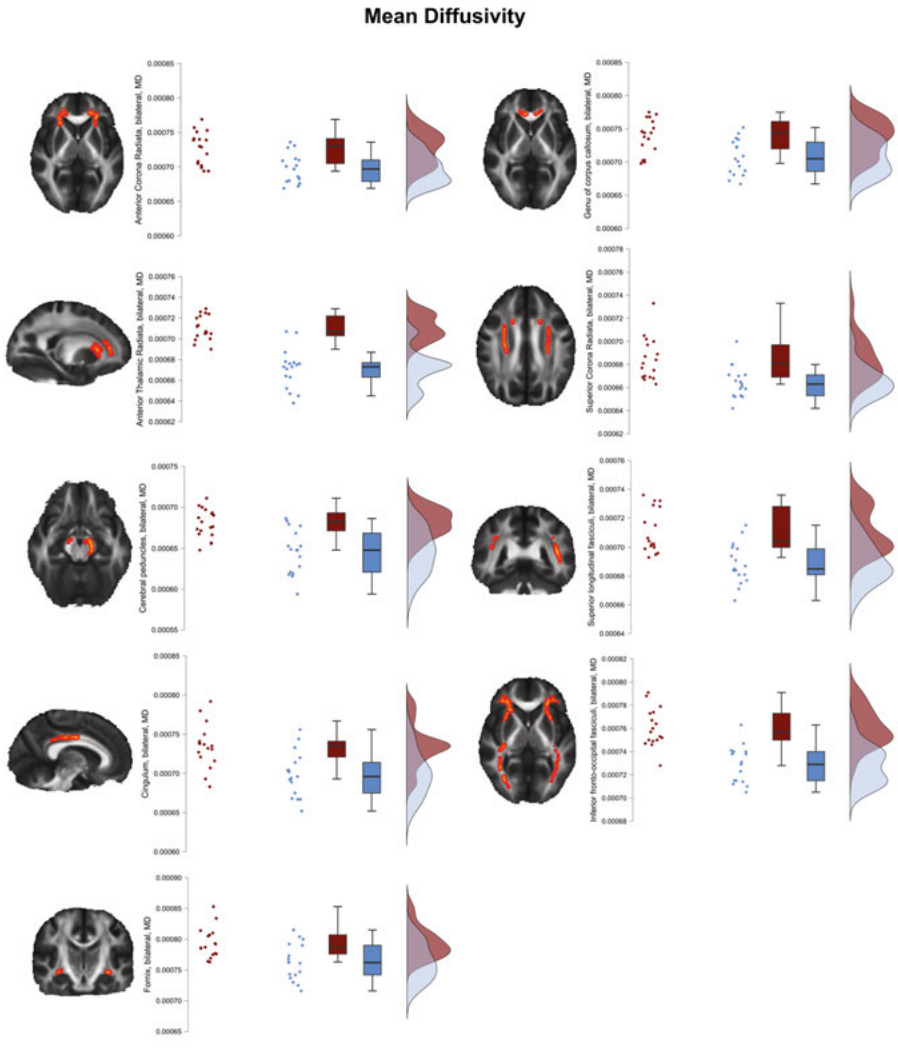

Figure 11. Whole-brain voxel-wise tract-based spatial statistics revealed SPRM and placebo treatment group cross-sectional differences at follow-up for mean diffusivity in the bilateral anterior corona radiata, anterior thalamic radiations, cerebral peduncles, cingulum, fornix, genu of corpus callosum, inferior fronto-occipital fasciculi, superior longitudinal fasciculi, and superior corona radiata.

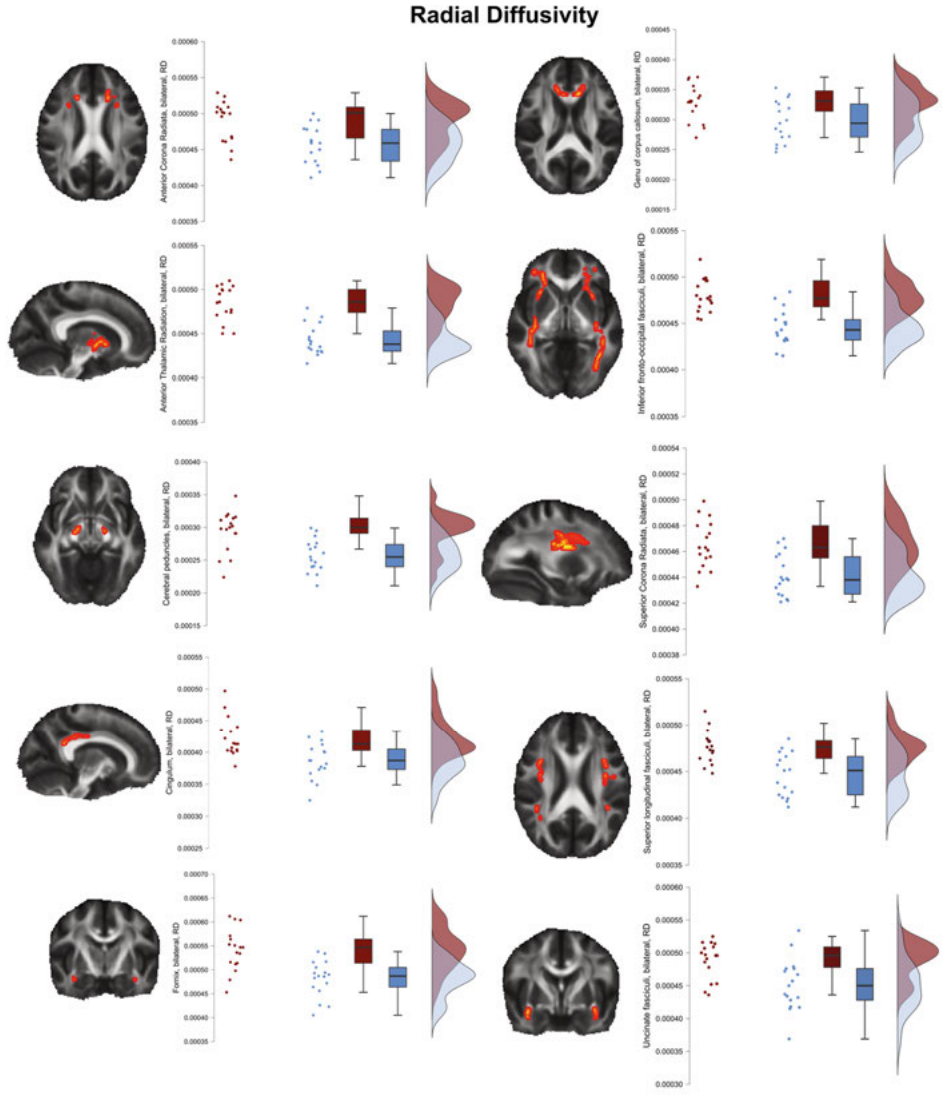

Figure 12. Whole-brain voxel-wise tract-based spatial statistics revealed SPRM and placebo treatment group cross-sectional differences at follow-up for radial diffusivity in the bilateral anterior corona radiata, anterior thalamic radiations, cerebral peduncles, cingulum, fornix, genu of corpus callosum, inferior fronto-occipital fasciculi, superior longitudinal fasciculi, superior corona radiata, and uncinate fasciculi.

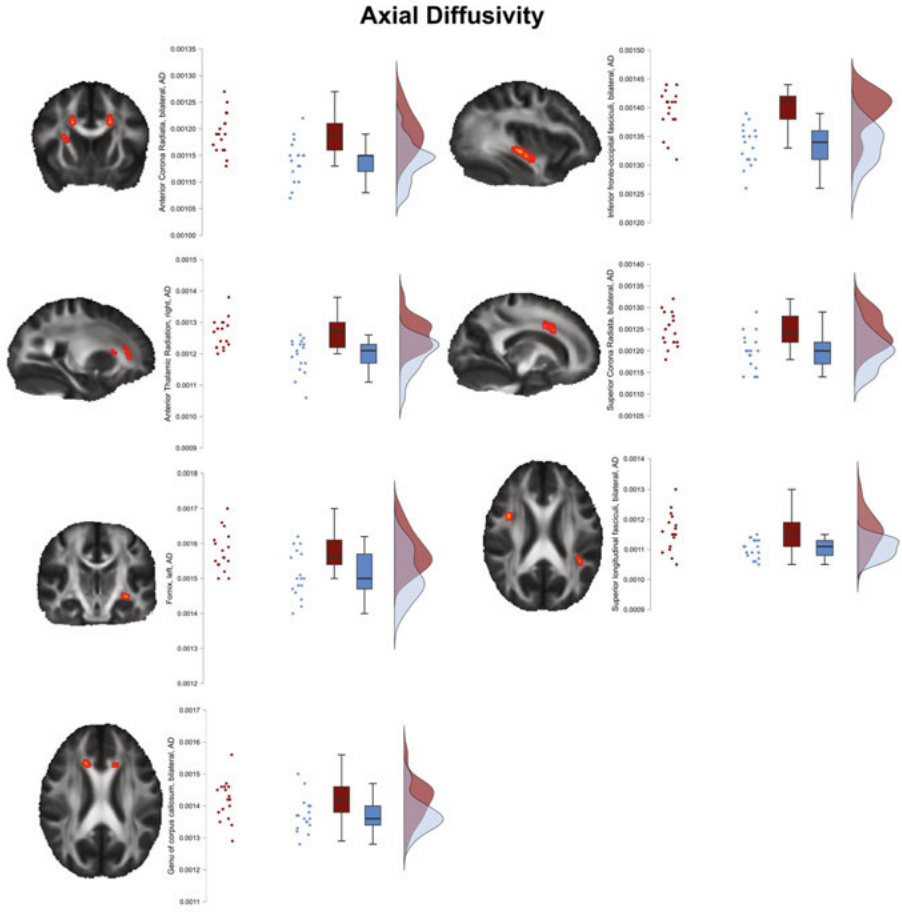

Figure 13. Whole-brain voxel-wise tract-based spatial statistics revealed SPRM and placebo treatment group cross-sectional differences at follow-up for axial diffusivity in the bilateral anterior corona radiata, genu of corpus callosum, inferior fronto-occipital fasciculi, superior corona radiata, superior longitudinal fasciculi, the right anterior thalamic radiation and the left fornix.

However, in a recent study that compared white matter microstructure between individuals with PMDD and healthy controls, significantly higher FA in the left uncinate fasciculus, as well as, albeit on a trend level, in the right uncinate fasciculus, the cingulum, genu of corpus callosum, and superior longitudinal fasciculus, reaching a suggestive statistical significance level (GU et al. 2022). With regard to the rest of diffusivity metrics, the authors did not report any further statistically significant results, although higher MD and AD was reported within the superior corona radiata, along with greater AD in the dorsal cingulum bundle, the superior longitudinal fasciculus, and the uncinate fasciculus, again at a trend level (GU et al. 2022). Given these findings, the SPRM group's lower FA and higher MD, RD, and AD could indicate a

potentially beneficial effect of SPRM on PMDD-specific white matter integrity signatures.

Study IV

The white matter volume correlates of three-month SPRM treatment were also explored in comparison to placebo. The application of voxel-based morphometry did not reveal any significant clusters, both when evaluating treatment by time effects within the apriori defined ROI masks and at a whole-brain level.

The impact of ovarian hormones on white matter in terms of neuroactivity is not well-documented. Existing literature primarily focuses on the effects of oestradiol on white matter integrity (DE BONDT *et al.* 2013; BARTH *et al.* 2016) and volume (MEEKER *et al.* 2020). Differences in white matter volume distinguishing individuals with PMDD from healthy controls have only recently been observed, with those with PMDD exhibiting larger white matter volume in the uncinate fasciculus (GU *et al.* 2022). The current findings argue against the hypothesis that changes in white matter volume are involved in the mechanism through which SPRM treatment ameliorated symptom severity (COMASCO *et al.* 2021). The absence of results could be ascribed to the duration of the treatment regimen, suggesting that three months might not have been sufficient to induce changes in white matter volume. However, the more plausible explanation is that SPRM treatment primarily influenced functional neural pathways (KALTSOUNI *et al.* 2021) rather than structural ones (KALTSOUNI *et al.* 2022).

Study V

Resting state functional dynamics were explored after three-month treatment with SPRM or placebo. Seed-based connectivity analyses unveiled interaction effects between time and treatment groups in the rs-FC of fronto-visual, temporo-insular, and temporo-cerebellar networks (Figure 14). The two groups did not differ at baseline, but did so at follow-up, when the rs-FC of the pSTG (posterior superior temporal gyrus) and insula decreased notably for the SPRM group, reaching levels significantly lower than those observed in the placebo group. Importantly, the decrease in cortisol levels was associated with decrease in connectivity in the SPRM group, implying beneficial treatment outcomes, given cortisol's involvement in stress response and cognitive processing. Altered functional activation patterns have been seen in both regions in individuals with PMDD compared with healthy samples (DUBOL *et al.* 2021). Insula is central to higher order cognition and emotional experience (UDDIN *et al.* 2017), the STG is known to play a role in sensory and language processing (BIGLER *et al.* 2007). Taken together, the decrease in rs-FC

between the regions, potentially relevant to sensory information processing, along with the association to cortisol levels imply beneficial effects of SPRM treatment on rs-FC.

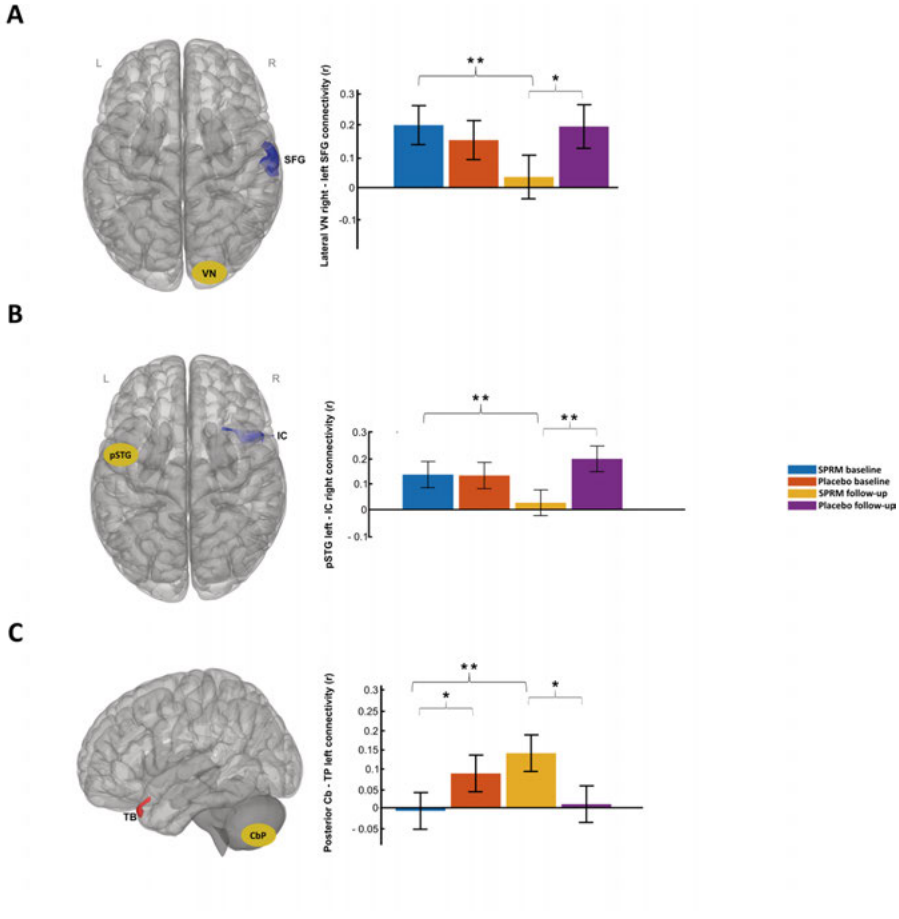

Figure 14. Seed-to-voxel analyses revealed treatment by time effects on resting state functional connectivity between: (A) a cluster in the left superior frontal gyrus (x: -16, y: 16, z: 62) and the right lateral visual network seed, (B) a cluster in the right insular cortex (x: 48, y: 14, z: -14) and the posterior superior temporal gyrus of the language network seed, and (C) a cluster in the left temporal pole (x: -36, y: 22, z: -24) and the posterior cerebellum seed. Clusters are false discovery rate corrected. Significant effects are depicted in bar graphs with 95% confidence interval error bars. Statistically significant post-hoc comparisons are noted on bar graphs. CbP: posterior cerebellum; IC: Insular cortex; LN: language network; pSTG: posterior superior temporal gyrus; SFG: superior frontal gyrus; TP: temporal lobe; VN: visual network. *: $p > 0.01$, **: $p > 0.001$

The connectivity between the right lateral visual network (VN) and the left superior frontal gyrus (SFG) experienced a significant post-treatment decrease

in the SPRM group, leading to a significantly lower level than in the placebo group at follow-up. Functional abnormalities have been shown in frontal and visual areas in PMDD (GAO *et al.* 2021). Even more recently, PMDD diagnosis and menstrual cycle phase were found to impact connectivity between the region and the left lateral occipital cortex (REUVENI *et al.* 2023). The SFG is central to cognitive control (HU *et al.* 2016) and part of the suggested regions included in the pathophysiology of PMDD (DUBOL *et al.* 2020) What is more, different GABA concentrations are documented in women with PMDD compared with controls in occipital regions (EPPERSON *et al.* 2002b). Additionally, in the placebo group, the decrease in right VN-right SFG coupling from baseline was positively correlated with reduction in total DRSP, irritability, and depression scores. Albeit preliminary, these results could hint the impact of SPRM treatment on regional connectivity underlying information processing and cognitive control. It is however important to be cautious with interpretations, as the correlation is present only in the placebo group and could thus be related to a placebo effect.

Conversely, there was a significant increase in rs-FC between the posterior cerebellum (Cb) and the left temporal pole (TP) from baseline in the SPRM group. Temporo-cerebellar rs-FC was also higher than in the placebo group at follow-up. There is evidence on differential temporal and cerebellar functioning between PMDD samples and controls (DUBOL *et al.* 2020), while the altered connectivity between the regions has been seen in depressive samples (LIU *et al.* 2012; DAI *et al.* 2023). Both regions are diverse in terms of function profile, involved in information integration and somatosensory processing to higher order cognition and affective regulation (SCHMAHMANN *et al.* 2007; HERLIN *et al.* 2021). Progesterone modulation seems to have had altered connectivity between the regions, although it is unclear if this is related to symptom relief. However, it is noteworthy that this connectivity was significantly lower at baseline, signifying pre-existing differences between the two groups before the initiation of treatment.

Neurobiological underpinnings of SPRM treatment

It is plausible to hypothesize that symptoms relief following SPRM treatment is due to the effect of allopregnanolone on corticolimbic function. Unfortunately, due to delays related to the pandemic, allopregnanolone data are not part of this thesis. One way progesterone exerts its action is indeed via allopregnanolone, its 3 alpha, 5 alpha downstream metabolite with primary anxiolytic effects (BITRAN *et al.* 1995). Indeed, it is temporally correlated with the onset of PMDD symptoms (BÄCKSTRÖM *et al.* 2014). Recent clinical trials using isoallopregnanolone, an endogenous allopregnanolone antagonist (BIXO *et al.* 2017; BÄCKSTRÖM *et al.* 2021) and 5α-reductace inhibitor (MARTINEZ *et al.* 2016), which blocks the conversion of progesterone to allopregnanolone,

demonstrated significant improvement of the mood symptoms in PMDD. Even if not yet well established, allopregnanolone production or metabolism changes are hypothesized to trigger the affective switch in PMDD (SCHILLER *et al.* 2014). More specifically, allopregnanolone functions as a positive allosteric modulator of the GABA subunit A ($GABA_A$) receptor (BELELLI AND LAMBERT 2005), which regulates inhibitory signaling in the mammalian brain (MILLER AND ARICESCU 2014). The interactions between steroids and the $GABA_A$ receptor are region- and neuron-specific and the main actions allopregnanolone has been shown to exert on the $GABA_A$ receptor are subunit composition, phosphorylation, along with effects on steroid metabolism (BELELLI AND LAMBERT 2005).

Two studies on PMDD using proton magnetic resonance spectroscopy, a non-invasive technique measuring *in vivo* brain biochemical changes, have demonstrated imbalances between the inhibitory GABA and the excitatory glutamatergic neurotransmission and differential cortical GABA levels in cases compared to controls (EPPERSON *et al.* 2002a; LIU *et al.* 2015). Evidence from postmenopausal women with intermediate allopregnanolone concentrations shows that negative affect was enhanced upon progesterone treatment compared to placebo or oestradiol (BRINTON *et al.* 2008). Hence, $GABA_A$ receptor subunit composition in response to allopregnanolone exposure is suggested as a biological marker for PMDD symptomatology, and not differential allopregnanolone level exposure on the $GABA_A$ receptors (HANTSOO AND EPPERSON 2020). Consequently, progesterone and neuroactive derivatives seem to be necessary for the symptom onset in conjunction with possible GABA sensitivity in PMDD women.

Additionally, oestradiol is a main component of symptom emergence, as evidence supports that not solely progesterone, but the oestradiol/progesterone ratio is central for symptom severity (SEGEBLADH *et al.* 2009). In fact, oestradiol is also important in the conversion from progesterone to allopregnanolone, as it can enhance the action of two enzymes that are involved in the conversion process in the pituitary gland and hypothalamus (CHENG AND KARAVOLAS 1973). Thus, maintaining allopregnanolone in stable and low levels seems to be seminal for symptom alleviation. The current studies did not involve assessments of allopregnanolone levels, but such analyses should be incorporated in future investigations.

Conclusions

This work presents the outcomes of a multimodal pharmaco-neuroimaging investigation aimed at elucidating the neural correlates of SPRM treatment in individuals diagnosed with PMDD. In general, the effects that SPRM treatment had on brain function indicate enhanced inhibitory processing, here in the context of reactive aggression (Paper I), along with altered resting state functional dynamics between regions involved in cognitive, affective, and sensorimotor processing (Paper V). Regarding brain structure, SPRM treatment did not exert an influence on grey matter (Paper II), white matter (Paper III), or cortical surface (Paper II). Nevertheless, cross-sectional differences in terms of white matter integrity were observed post-treatment across various white matter tracts throughout the brain. While the observed pattern of differences, specifically lower FA and higher MD, RD, AD, is not immediately interpretable, it suggests the possibility that either an inflammatory response occurred following the treatment or that SPRM treatment influenced the white matter integrity correlates specific to the luteal phase.

In summary, the key findings of all papers can be outlined as follows:

- The SPRM group showed lower mood symptom severity upon treatment with SPRM compared to the placebo group.
- In a task involving reactive aggression, individuals with PMDD exhibited heightened functional reactivity in a cluster that extended across the dorsomedial PFC and dorsal ACC during the aggressive response condition.
- Although not statistically significant, there was a trend indicating reduced fronto-cingulate functional activation in the placebo group, which correlated with a higher frequency of aggressive responses. In terms of behaviour, the two treatment groups did not exhibit discernible variations, as there were no differences between the two groups in the frequency of aggressive responses or in overall aggression.
- No significant treatment group-related changes over time were observed in GMV, WMV, and cortical surface measures. In line with this, no correlations between change in brain structure metrics and symptom severity change from baseline were found.
- No longitudinal differences in white matter integrity were detected between the treatment groups. However, the SPRM treatment group

had lower FA and higher MD, RD, and AD within the anterior corona radiata, anterior thalamic radiation, cerebral peduncle, cingulum, fornix, genu of the corpus callosum, inferior fronto-occipital and superior longitudinal fasciculi, anterior thalamic radiations, along with higher RD in the uncinate fasciculi. No associations between white matter integrity and symptom severity were noted.

- Administration of SPRM, as opposed to a placebo, impacted resting-state functional coupling. The SPRM group exhibited reduced fronto-occipital and superior temporo-insular coupling, while an increased temporo-cerebellar rs-FC was observed from baseline to follow-up.
- Positive correlations between change in functional coupling between the lateral VN and the SFG and change in total and mood symptom severity were observed only in the placebo group. In contrast, change in connectivity between pSTG and IC was positively linked to cortisol level changes in the SPRM group.

Collectively, these findings indicate that SPRM treatment yielded mainly functional effects, by contributing to enhanced inhibitory control, mediated by the dorsal control system. Additionally, it influenced resting state networks involved in higher order cognitive function, language processing, as well as affective and sensorimotor function. Regarding structure, the sole structural associations with progesterone modulation were observed in white matter integrity, revealing a pattern that was either detrimental or specific to PMDD.

The present results are important in understanding the neurobiological underpinnings of PMDD symptom occurrence. Taken together, these findings support the hypothesis that fluctuations, rather than absolute hormonal levels, particularly progesterone, are likely the primary contributors to premenstrual symptomatology, potentially through endocrine-state-dependent functional neural states. This perspective finds support in, among others, a study from 2017 demonstrating that the abrupt decline in progesterone, along with individual progesterone kinetics, plays a crucial role in the manifestation of premenstrual symptoms (LOVICK *et al.* 2017). In the domain of neuroimaging research, while not specifically studied in PMDD samples, evidence from dense sampling of functional connectivity data provides support for the concept of dynamic organization and flexibility in functional networks, contingent on simultaneous fluctuations of ovarian hormones (PRITSCHET *et al.* 2020; MUELLER *et al.* 2021; GREENWELL *et al.* 2023). Such alterations in network flexibility have been connected to affect, confirming the hypothesis that phase-related functional organization could be pivotal in the manifestation of symptoms (BETZEL *et al.* 2017). It is therefore likely that three-month progesterone modulation altered the functional dynamics between regions relevant to premenstrual symptomatology.

Methodological Considerations

In the absence of an established neurobiological profile for PMDD, it has been challenging for clinicians and researchers to establish diagnostic and research procedures on menstrual related mood disorders (HALBREICH 2004). The dichotomy between premenstrual syndrome and PMDD has not been properly clarified in the past and the recognition of PMDD as a diagnostic entity is rather recent (EPPERSON AND HANTSOO 2017). Specifically, for PMDD, the diagnosis is based on prospective for at least two menstrual cycles in order to assess premenstrual symptoms and confirm PMDD symptomatology (A.P.A. 2013). Here, we used the DRSP, which is one of the most validated prospective ratings instruments (NEVATTE *et al.* 2013). Recently, a new instrument, the Carolina Premenstrual Assessment Scoring System (C-PASS) was developed by Esenlohr-Mour and colleagues (EISENLOHR-MOUL *et al.* 2017). The C-PASS constitutes a scoring system for the DRSP ratings that sought to simplify the diagnostic procedure based on the DSM-5 criteria, while increasing the accuracy in distinguishing women that meet the full criteria for PMDD diagnosis from those suffering from the premenstrual syndrome or other disorders. In all papers included in this thesis, the symptom severity outcome variables considered were the premenstrual DRSP total score, along with the four subscales that correspond to the PMDD core symptoms according to DSM-5 and as described in (EISENLOHR-MOUL *et al.* 2017). Because the summed total score has been characterized as less sensitive in capturing change in severity (EISENLOHR-MOUL *et al.* 2016), the present studies also took into account the application of the DSM-5 criteria to the core affective symptoms, thus offering a more precise interpretation of the relationship between marked affective symptom severity and brain function or structure.

An important point is that the mood symptoms included in the diagnosis of PMDD can differ in terms of predisposing risk factors and biological factors. Such differences are likely to be instrumental in treatment efficacy. According to recent findings, mood rather than physical symptoms, especially irritability and mood swings, were found to be the most common premenstrual symptoms causing significant impairment (ERIK STUDER *et al.* 2023). Although the relationship between DRSP symptom severity and the various brain measures was assessed in the present work, it cannot safely be excluded that different structural or functional mechanisms are involved in each symptom or specific groups of symptoms. That is because relevant analyses could not be

implemented due to the modest sample size along with the fact that there was not a large variation in symptom severity in the current sample.

Concerning the fMRI study, the fact that there was no "clean" baseline condition, such as a fixation cross, is one of the design's main limitations. As mentioned in the paper, this combined with a moderately aggressive sample and no distinction between low and high provocation conditions, could potentially explain the lack of findings on limbic reactivity and cortico-limbic connectivity. In studies using other aggression paradigms, such as the Taylor Aggression Paradigm (TAP), in a high provocation context, reactivity in the amygdala and right anterior insula, along with rostral and dorsal ACC, was observed when comparing the fair and unfair opponent in healthy individuals, probably due to the stronger involvement of emotion-related ROIs, as the authors speculate (KRÄMER *et al.* 2008). More research is thus needed to confirm and expand on our findings.

A big chapter in assessing the brain correlates of affective disorders includes issues that begin from data acquisition extending to data analysis software and method heterogeneity, amongst others (NICHOLS *et al.* 2017). For instance, the algorithms behind brain measurement computations can differ significantly according to the software or version of it. Be it as it may, in order to ameliorate inconsistencies, transparent reporting is essential. In the case of this thesis and with a reference to the first paper (KALTSOUNI *et al.* 2021), our initial result from the separately tested PFC and ACC ROIs, indicated two clusters as significantly modulated by SPRM treatment. However, due to the anatomical proximity of the two regions, we conducted the analysis again within a ROI mask that contained both regions, demonstrating that the observed effect was one. Such matters are not uncommon in neuroimaging studies. In the same spectrum of challenges, a VBM study exploring grey matter differences between women with PMDD and healthy controls reported a hippocampal and a parahippocampal cluster demonstrating differential grey matter morphology between the two groups (JEONG *et al.* 2012). However, they followed solely a whole-brain approach and the reported results are considered significant at $p < 0.001$ uncorrected level, which, although not uncommon, renders the findings less reliable considering the large number of statistical tests performed over the whole brain in each voxel (RIDGWAY *et al.* 2008). Correct and universal reporting guidelines in neuroimaging studies is a matter that is gaining increasing attention and evolving fast (POLDRACK *et al.* 2008; RIDGWAY *et al.* 2008; NICHOLS *et al.* 2017).

It is important to interpret the results in the light of the limitations of the functional neuroimaging studies on PMDD regarding sample size and statistical power, which might have played a role in possible false relationships and false positive or negative effects (DUBOL *et al.* 2020). While all studies included rather few participants, most used small volume correction to account for the multiple testing problem (PROTOPOPESCU *et al.* 2008; GINGNELL *et al.* 2012; GINGNELL *et al.* 2013; GINGNELL *et al.* 2014) and one used Bonferroni

correction (PETERSEN *et al.* 2018). In the current thesis, correcting for multiple testing was applied, although in some instances, the threshold was more lenient due to the novelty of the studies and the modest sample size.

One of the noteworthy limitations of the selected methods is the limited spatial normalization accuracy of the VBM technique as inter-subject variability variations are not fully accounted for (RIDGWAY *et al.* 2008). Additionally, since VBM offers a gross volumetric estimation of grey matter volume, interpretation issues arise, as it is not possible to distinguish thickness from surface area changes. To avoid the shortcomings of possible template effects on our results and overcome interpretation challenges, we combined VBM with SBM, as the latter provides additional morphological measures. Furthermore, as accuracy varies between brain structures, we employed an additional subcortical segmentation pipeline, to provide more fine-scale anatomical localisation of the subcortical structures. Regarding TBSS, it is also worth mentioning that despite its advantage over VBM in mitigating misalignment issues. The main criticism brought up concerns the difficulty in distinguishing of adjacent or crossing white matter bundles, due to the method's use of FA maps and thus the fact that bundle orientation is not regarded (BACH *et al.* 2014).

Lastly, concerning the study framework, the double-blind randomized control design, along with prospective and digital measurement of symptom severity are two main factors increasing robustness. However, SPRM treatment can cause amenorrhea in some women, which likely led to unblinding (COMASCO *et al.* 2021). Regarding the hormone analyses, allopregnanolone data was not yet available and will be investigated in relation to both brain structure and function within the PSAP paradigm.

Ethical Considerations

All study recruitment procedures followed the guidelines Declaration of Helsinki guidelines and received approval by the Uppsala ethics committee (Dnr. 2016/184) and the Medical Products Agency in Sweden, EUDRA-CT 2016-001719-19 approved all study procedures. All women received written informed consent along with oral information and introduction to the study before signing. All studies abide to the principles stated in the Declaration of Helsinki for good medical research involving human subjects. Women in both studies were fully informed about the research goals and proceedings and participated voluntarily and they were informed of their freedom to terminate their participation at any stage of the study. Participants' concerns about confidentiality and data anonymity matters were addressed. Data are safely stored and anonymized and results in line with the General Data Protection Regulation and they are only presented at a group level.

Women with PMDD experience significant suffering for a great part of their childbearing age and no treatment or technique is universally effective for all women. Thus, it is not uncommon that women are entering a study seeking improvements in the quality of their daily lives via symptom amelioration. In view of this, the main characteristic of randomized-control trials is that a part of the sample of recruited women is going to receive the treatment and the rest an inactive substance. It is of great importance that women understand the nature of the study and the possibility of receiving the placebo pill, so clinicians verbally ascertained the participants fully understood the study design. Regarding treatment safety, UPA is not an approved treatment for PMDD, yet the drug is widely used for the treatment of uterine fibroids and has demonstrated a generally safe profile (RABE *et al.* 2018). However, due to the report of severe cases of liver injury, administration guidelines have been put forward by the European Medicines Agency (EMA) to reduce such risks. In the proof-of-concept clinical trial assessing the efficacy of UPA in PMDD, women underwent liver function tests and no particular side effects emerged (COMASCO *et al.* 2021). Finally, concerning the safety of the MR scanner, all procedures adhere to the regulations established by the Department of Radiology at Uppsala University Hospital. These procedures involve minimal risk and are standard in routine examinations. Additionally, the research nurses and responsible researchers conducting the scans are adequately trained. However, if the participants experienced any form of discomfort, the scanning session was immediately interrupted or stopped.

Future Perspectives

As inferred from the current results, it is possible that the mechanism explaining PMDD symptom relief exists at a functional level. The results of Study I partly confirmed the cortico-limbic dysfunction hypothesis underlying affective symptomatology, as stable hormone levels seemed to enhance cognitive control. Resting state dynamics were influenced by SPRM treatment, providing a less clear account for understanding its relevance to PMDD. However, these changes indicate potential positive effects on network connectivity related to cognition and affect. Although there were no apparent changes in grey and white matter volume or cortical architecture due to progesterone modulation, SPRM showed widespread effects on white matter integrity.

Given the novelty of the current work, caution is required when drawing conclusions about the biological effects of progesterone modulation effects on PMDD. Despite several studies delving into the neuromolecular underpinnings of PMDD pathophysiology, there remains a substantial gap as regards understanding effective interventions and elucidating their neurobiological mechanisms.

As in other psychiatric disorders, disentangling the causes of symptom occurrence and severity is a complex endeavour. The fields of neuroscience and psychiatry have begun acknowledging that psychiatric symptoms are a matter of multidimensional systems rather than single biomarkers. Consequently, symptom relief is likely the result of a combination of interconnected and interacting factors. When it comes to menstrually related mood disorders such as PMDD, unravelling the mechanistic nature of the disease becomes even more complicated due to the relationship between the endocrine and neural system, and their chronobiologic interactions (HAUS 2007). Pharmacological treatments such as SSRIs, which have been in use for decades, appear to exhibit different effects on PMDD compared to other mood disorders like depression, particularly in relation to the timing of action and effectiveness (MARJORIBANKS *et al.* 2013).

Based on the current findings, it appears that progesterone also exerts modulatory effects on the intrinsic organization of neural networks. It is not unlikely that fluctuating endocrine states are related to variations in functional neural states, which might be of particular importance in PMDD due to the hypothesized neural susceptibility to the hormonal states. Indeed, progesterone seems to be able to dynamically modulate brain organization throughout the cycle (ARÉLIN *et al.* 2015). There is preliminary evidence distinguishing

individuals with PMDD from healthy controls in terms of functional connectivity (DUBOL *et al.* 2020), although more recent results suggest that such alterations are steady throughout the cycle (DAN *et al.* 2020). Recently, a critical review of electrophysiological findings related to menstrually related mood disorders offered an initial suggestion of underlying spontaneous frontal activity differences between cases and controls, although direct links to endocrine states and hormonal profiles are contradictory (KALTSOUNI *et al.* 2024). Therefore, it is essential to further specify the mechanism by which properties of network organization might be related to hormonal fluctuations and the onset of symptoms.

At a neurobiological level, it is crucial to expand mechanistic evidence related to hormonal manipulation in PMDD, with a specific emphasis on unravelling the individual effects of hormones on symptom severity. Given the high effectiveness of progesterone modulation in psychological symptom relief (COMASCO *et al.* 2021), it is imperative to delineate the specific changes in metabolic pathways, neurotransmission, and neuroplasticity. Here, we provide a preliminary indication of SPRM-mediated enhanced cognitive control. Consequently, additional investigations are required to characterize the pathways of disrupted emotional regulation in PMDD. Furthermore, because the structural correlates of PMDD are not entirely defined, there is a need for additional research to characterize PMDD-specific features of ovarian hormone effects at the microcellular level.

Regarding neurotransmission systems, alteration in $GABA_A$ receptor expression due to the withdrawal of progesterone and allopregnanolone has been exhibited (SMITH *et al.* 1998). GABAergic receptor function and expression under progesterone manipulation ought to be further specified *in vivo* to determine whether $GABA_A$ receptor sensitivity, composition, or any other aspect is implicated in premenstrual symptomatology. Indeed, women with PMDD are more susceptible to startle responses, a proxy measure of GABA function (SIKES-KEILP AND RUBINOW 2023). Current empirical evidence supports GABAergic function alone or in combination with serotonergic function as a candidate pathway of symptom relief (SCHWEIZER-SCHUBERT *et al.* 2020; SIKES-KEILP AND RUBINOW 2023). In healthy female individuals, down-metabolites of progesterone, such as allopregnanolone, have been shown to be associated with serotonergic function (SUNDSTRÖM POROMAA *et al.* 2018), offering an intriguing interplay to explore in the context of PMDD. Further research is warranted to gain further insights into the potential involvement of GABA-mediated pathways in relation to premenstrual mood symptoms.

From a neuropsychiatric standpoint, factors like early life stress and trauma are potential contributors to the onset of mood disorders (ESER *et al.* 2006; YANG *et al.* 2022; NAYMAN *et al.* 2023). This connection has also been found to be relevant to other reproductive disorders (BERTONE-JOHNSON *et al.* 2014; CROWLEY *et al.* 2015; GELAYE *et al.* 2016). Given the correlation between psychological stress and both endogenous and exogenous progesterone

(SMITH *et al.* 1998; DEVALL *et al.* 2009), it is necessary to further clarify the relationship between progesterone and stress response signalling and psychosocial stress trajectories in PMDD.

Considering the burden of illness related to PMDD (RAPKIN AND WINER 2009) along with the high suicide risk among PMDD sufferers (WIKMAN *et al.* 2022), further rigorous research is needed to shed light on symptom pathophysiology. More randomized control trials, as well as longitudinal and dense-sampling studies, are required to provide a broader account of neurobiological components, functional dynamics, and risk factors that contribute to this neural susceptibility to ovarian hormones.

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