Therapieansprechen bei Endometriose

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Inhaltsverzeichnis

Publikationen Luisa Karolina Maulitz

Publikationen, die die Dissertation darstellen

Maulitz, L., Stickeler, E., Stickel, S., Habel, U., Tchaikovski, S. N., & Chechko, N. (2022). Endometriosis, psychiatric comorbidities and neuroimaging: Estimating the odds of an endometriosis brain. *Frontiers in neuroendocrinology, 65,* 100988. https://doi.org/10.1016/j.yfrne.2022.100988

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Weitere Publikationen

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Endometriosis, psychiatric comorbidities and neuroimaging: Estimating the odds of an endometriosis brain

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ABSTRACT

Endometriosis is a chronic pain disorder that affects young women, impairing their physical, mental and social well-being. Apart from personal suffering, it imposes a significant economic burden on the healthcare system.

We analyzed studies reporting comorbid mental disorders in endometriosis based on the ICD/DSM criteria, discussing them in the context of available neuroimaging studies.

We postulate that at least one-third of endometriosis patients suffer from mental disorders (mostly depression or anxiety) and require psychiatric or psychotherapeutic support. According to three neuroimaging studies involving patients with endometriosis, brain regions related not only to pain processing but also to emotion, cognition, self-regulation and reward likely constitute the so-called "endometriosis brain". It is not clear, however, whether the neurobiological changes seen in these patients are caused by chronic pain, mental comorbidities or endometriosis itself.

Given the paucity of high-quality data on mental comorbidities and neurobiological correlates in endometriosis, further research is needed.

1. Introduction

Endometriosis is a chronic inflammatory disease characterized by lesions of endometrium-like tissue outside the uterus. The leading symptoms of the condition, which has the potential to result in infertility (Siedentopf & Sillem, 2014; World Health Organization, 2020), are chronic pelvic pain (CPP), painful menstruation or intercourse, and painful or difficult urination or defecation. Long seen as a local disease (Benagiano & Brosens, 1991), its treatment has been limited to the surgical removal of the lesions. Increasingly, the combined treatment of laparoscopic removal of endometriosis followed by three- to six-month endocrine therapy is found to yield the highest response rates (Mettler et al., 2014). Nevertheless, the majority of patients require longer-term treatment to control the persistent pain symptoms, which reoccur after discontinuation of endocrine therapy (Vercellini et al., 2003). Irrespective of the treatment approach, however, over 50% of women suffer a recurrence of the disease over a period of 5 years (Zondervan et al., 2020). The fact of frequent symptom recurrence after (repeated) surgical therapy, and the current advances in the disease pathophysiology and neuroscience have led to the general acceptance of endometriosis as a systemic disease, involving not only local changes but also those in the endocrine and central nervous systems (Bulun et al., 2019; Zondervan et al., 2020). Given the problems of CPP, infertility, and lack of satisfaction with the quality of life, women suffering from endometriosis constitute a high burden of psychosocial load, often resulting in mental disorders with varying degrees of severity.

1.1. Prevalence and pathophysiological mechanisms

Increasingly understood as a result of complex interactions of immunological, genetic, hormonal and environmental factors (Toth, 2010; Bulun et al., 2019; Zondervan et al., 2020), endometriosis is

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among the most frequent non-malignant diseases in women of childbearing age (Eskenazi & Warner, 1997), affecting about 10% of all reproductive-age women (Shafrir et al., 2018). However, the true prevalence of the disease may be underestimated as the percentage of women who have endometriosis but are asymptomatic is unknown. That means that our knowledge of population distributions, disease manifestations, and risk factors of endometriosis is limited to the data involving women in whom endometriosis is a) clinically manifested (usually via pain and/or infertility) and b) successfully diagnosed via surgical visualization and histological examination of the removed endometriotic lesions (Zondervan et al., 2020).

The pathophysiological mechanisms leading to the establishment of ectopic endometrium lesions outside the uterus, as a histopathological substrate for endometriosis, have yet to be elucidated. The most frequently cited theory, and the one most supported by evidence thus far, is Sampson's theory of transplantation and implantation (Sampson, 1927), which suggests that endometriosis implants originate from eutopic endometrium alighting in the abdominal cavity during retrograde menstruation (Zondervan et al., 2020; Bulun et al., 2019). However, given that retrograde menstruation is common, affecting up to 76–90% of menstruating women (Blumenkrantz et al., 1981; Carpinello et al., 2021), there must be other factors that enable endometrial cells to adhere to peritoneal surfaces, survive, proliferate, and develop into endometriotic lesions. Increased production of estrogens, cytokines, prostaglandins, and metalloproteinases, local progesterone resistance, enhanced angiogenesis and immune dysfunction have been demonstrated to facilitate the survival and proliferation of the ectopic endometrial tissue (Bulun et al., 2019).

1.2. From the ectopic endometrial tissue to memories of pain in the cerebral cortex

In women with endometriosis, the severity of the symptoms correlates poorly with the extent of the disease. While women with a small number of lesions and few adhesions may suffer severe pain or infertility, or both, those with more lesions and/or endometrioma, along with extensive adhesions, may be asymptomatic (Zondervan et al., 2020). The reason behind that, and the persistent pain even after the removal of endometriotic lesions, is that pelvic pain may be both inflammatory and neuropathic in nature (Carey et al., 2017), both (particularly the latter) being characterized by potential sensitization of the central nervous system (Laux-Biehlmann et al., 2015), which is also thought to be the case in other chronic pain conditions such as fibromyalgia or chronic spinal pain (Malfliet et al., 2018; Petzke et al., 2003).

The complex endocrine and proinflammatory microenvironment in and around the endometriosis lesions promotes their proliferation, vascularization and nociception (Laux-Biehlmann, 2015). The endometrium-like tissues release a number of inflammatory proteins and chemokines, which induce leukocyte activation and macrophage recruitment, subsequently stimulating neuroangiogenesis in the endometriosis lesions. The nerve fiber density in the lesions is associated with pain severity, which can be reduced by hormonal therapies, providing one of the possible mechanisms for the pain relief experienced during hormonal treatment (Asante & Taylor, 2011). The nerve fibers within endometriotic lesions (Berkley et al., 2005) are permanently stimulated by inflammatory mediators and nerve-sensitizing proteins, which are released by noxious stimuli into the sensory afferent nerve at the lesion's distal end with the nociceptive signal being transferred to the nerve root of the dorsal horn of the spinal cord (Laux-Biehlmann, 2015). Moreover, nociceptive channels, including a number of neuropeptides playing a key role in generating hyperalgesic responses, have been seen to be overexpressed in endometriosis lesions (Saunders & Horne, 2021). The pain signal is conveyed to the thalamus, the brain stem and the cerebral cortex (Bulun et al., 2019; Laux-Biehlmann et al., 2015; Zondervan et al., 2020). This persistent stimulation of the lesion sites by the inflammatory factors induces a structural remodeling of the peripheral synapses, resulting in accelerated conduction along the nerve fibers (Zheng et al., 2019). Additionally, the persistent nociceptive input may increase the responsiveness of the dorsal horn neurons, and the processing signals from the visceral and somatic tissues, leading to a reduction of the pain threshold and exaggeration of pain perception (Bajaj et al., 2003). More salient pain signals are conveyed to the thalamus where they are further processed with respect to their sensory and affective qualities. Notably, brain changes in patients with chronic pain are not limited to the nociceptive pathways; they also involve the mesocorticolimbic circuitry, which is primarily linked to motivation, reward, aversion and learning processes (Barroso et al., 2021). The involved brain regions, like the anterior cingulate cortex, the medial prefrontal cortex (mPFC) and the amygdala, are thought to modulate the affective features of pain signals. Additionally, the hippocampus, classically associated with memory and learning processes, has also been demonstrated to undergo structural and functional changes, possibly due to pain-related memories with continual reinforcement and learning, which is caused by the constant presence of pain. In patients with chronic pain, these regions are functionally reorganized to acquire this abnormal network state, resulting in pain chronization (Apkarian et al., 2009; Barroso et al., 2021). These processes contribute to the generation of more intense pain memories in the cerebral cortex, exacerbating future experience of pain (Zondervan et al., 2020) and resulting in central sensitization. The fact that these processes are independent of the type of the disease and its stage of progression may be a partial explanation of the poor correlation between the severity of endometriosis and its clinical symptoms. It may be *central sensitization* (Berkley et al., 2005) that makes the sensation of pain in endometriosis extend beyond the endometriotic lesions, rendering patients highly susceptible to cross-organ sensitization (pain perception in adjacent structures due to the convergence of neural pathways) and causing inadequate pain relief in many cases even after a complete excision of the endometriosis loci (Zondervan et al., 2020).

1.3. From chronic pain to multifactorial burden

The clinical symptoms of endometriosis include not only chronic pain but also fatigue and infertility, affecting the physical, mental, sexual and social well-being of women with symptomatic endometriosis (Gallagher et al., 2018; Nnoaham et al., 2019; Rush et al., 2019; Zondervan et al., 2020). Not being able to sustain or regularly attend full-time work due to the symptoms of endometriosis, women frequently develop feelings of guilt. Also, the fear of stigmatization involving menstruation-related symptoms (Matasariu et al., 2017) keeps women from talking about the disease (Rush & Misajon, 2018), thus depriving them of the necessary social support. Women suffering from dyspareunia (painful intercourse) due to endometriosis demonstrate decreased sexual activity, self-esteem and sexual satisfaction (Brandes, 2007; De Graaff et al., 2016; Zondervan et al., 2020). Frequently, they also develop negative thoughts about intercourse and avoid sexual activity (Fritzer et al., 2013). The inability to conceive, or concerns about potential infertility, can further exacerbate the psychological distress. Collectively, these factors can seriously affect relationships (Shum et al., 2018), in some cases leading to their termination (Fagervold et al., 2009). At the same time, many women assume that their pain is normal and not pathological (Markovic et al., 2008), which is indirectly endorsed by their general practitioners and even gynecologists, who do not acknowledge the severity of the pain symptoms. All this often leads to a lengthy interval, ranging between seven and twelve years depending on the country, between the onset of symptoms and diagnosis (Fritzer et al., 2012; Ghai et al., 2019; Hadfield et al., 1996). This diagnostic delay and the ensuing lack of timely treatment likely affect the course of the disease, resulting in the persistence of the pain symptoms. Stress levels (Lazzeri et al., 2015) and perceived psychological impairment (Eriksen et al., 2008) increase with pain severity, putting women with endometriosis in a vicious cycle of pain, chronic distress,

physical inactivity and consequent physical deconditioning, and depressive mood and anxiety, each reinforcing the other (Petrelluzzi et al., 2012).

1.4. Preexisting factors increase the vulnerability

Given that adolescence and young adulthood is when the onset of endometriosis-associated pain symptoms is most often reported, the initial pathophysiological phases of endometriosis likely occur earlier in life (Zondervan et al., 2020). Interestingly, early stressful life events such as physical and sexual abuse during childhood and later in life, which are well-known risk factors for depression and anxiety disorders (Bernet & Stein, 1999; Spila et al., 2005), are also associated with an increased risk of endometriosis (Harris et al., 2018). There is some evidence that sexual and emotional abuse may have a greater influence on the development of endometriosis symptoms than physical maltreatment (Liebermann et al., 2018). Early psychological trauma is thought to cause persistent central pain sensitization with an enhancement of the nociceptive neuronal pathways via reduced inhibition, increased synaptic efficacy and membrane excitability (Woolf, 2011). Besides, exposure to stressful life events has been shown to cause changes in cortisol levels (Fries et al., 2005; Heim et al., 2000), in turn facilitating a secondary hypocortisolism, leading to an altered inflammation response and contributing to the development of endometriosis. In line with this hypothesis, women with endometriosis have been found to have lower levels of cortisol (Petrelluzzi et al., 2012). In addition, the early onset of pain symptoms in women with endometriosis, e.g. in adolescence (with the onset of menarche), likely affects the central nervous system, given its plasticity, leading to changes in brain structure (Brawn et al., 2014). There are other developmental and physiological factors, including an early menarche, shorter cycle, longer menstruation (factors increasing exposure to retrograde menstruation) as well as low birth weight and lower body-mass index (Eskenazi & Warner, 1997; Liu & Zhang, 2017; Shafrir et al., 2018; Zondervan et al., 2020), that have been found to be associated with an increased risk for endometriosis.

Personality traits also appear to influence the outcome of patients with endometriosis. For instance, patients with neurotic personality traits are more prone to developing chronic pain conditions, which can contribute to the development of symptomatic endometriosis (Charpidou, 2014). However, changes in personality traits can also occur secondary to the development of the symptoms of endometriosis. Women with painful endometriosis, for example, have been found to have lower levels of novelty seeking, higher harm avoidance and lower exploratory excitability and responsibility along with lower self-directedness compared to controls (Facchin et al., 2017). Moreover, patients with endometriosis are prone to pain catastrophizing (a negative cognitive-affective response to anticipated or actual pain). Their fear of pain and hypervigilance with respect to pain characteristics (van Aken et al., 2017) lead to a further increased perception of pain severity (Allaire et al., 2018). Thus, in addition to such factors as inflammation or alterations in pain processing, there are several biopsychosocial risk factors associated with the development of endometriosis and its complex symptomatology. It is difficult to determine whether these associations play a causal role in endometriosis, or whether they are consequences of the condition, due to our limited understanding of the disorder's initiation and development and the inability to diagnose it before symptom onset (Zondervan et al., 2020).

1.5. From multifactorial burden to psychiatric disorder and the endometriosis brain

Given the complex psychosocial burden of endometriosis, it is not surprising that several studies have found women with endometriosis to report depressive and anxiety symptoms more often, the relationship having also been observed in other chronic pain conditions like fibromyalgia, chronic lower back pain, migraine and myofascial pain (Bernik et al., 2013; Charpidou, 2014; De Graaff et al., 2016; Facchin et al., 2017; Lagana` et al., 2018; Luisi et al., 2015; Muchanga et al., 2017; Peres et al., 2017; Tagliaferri et al., 2020). However, most of the available studies on psychopathological comorbidities of patients with endometriosis are based on patients' self-reported data and questionnaires (e.g. Ek et al., 2018; Facchin et al., 2015; Lagana` et al., 2015), which leave a lot of room for misinterpretation or misunderstanding of items by the patients and cannot capture an individual's particular context and situation around possible symptoms (Pettersson et al., 2015; Saez-Flores et al., 2018; Serra et al., 2017). Thus, the prevalence rates of mental disorders in patients with endometriosis are likely to have been overestimated by the studies relying only on questionnaires and self-reporting outcomes (Levis et al., 2019). As a consequence, it is difficult to determine which percentage of women with endometriosis who report increased anxiety or depressive symptoms really meet the diagnostic criteria (e.g. Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Statistical Classification of Diseases and Related Health Problems (ICD)) for psychiatric disorders and require relevant treatment.

In addition, chronic pain, which is the leading symptom of endometriosis, can induce new mental disorders or aggravate preexisting ones (Pope et al., 2015; Roth et al., 2011). According to several *meta*-analyses, pain as well as depressive and bipolar disorders cause changes in regional brain morphology and functional connectivity (Coppieters et al., 2016; Iwabuchi et al., 2015; Kaiser et al., 2015; Schmaal et al., 2017; Smallwood et al., 2013; Wise et al., 2017). Given that, in addition to chronic pain, many women with endometriosis suffer from comorbid mental disorders, they likely undergo structural and functional changes in the brain. However, the exact extent of research in this field is unclear, having never been reviewed before, particularly in relation to psychiatric comorbidities. In the present review, we have sought to analyze the available data on the prevalence of common mental disorders among women with endometriosis based only on studies in which the diagnosis of mental disorders was objectively confirmed according to the ICD (World Health Organization, 2020) or the DSM (American Psychiatric Association, 2013) criteria. While self-reported questionnaire-based diagnostics of mental disorders has been demonstrated to have a high sensitivity, its specificity in comparison to a diagnostic interview is relatively low with a considerable probability of overestimation of the psychiatric symptoms (Thombs et al., 2018). While most other reviews have dealt with one psychiatric problem potentially associated with endometriosis (e.g. bipolar disorders or depression/anxiety) (Aerts et al., 2018; Dinsdale & Crespi, 2017; Gambadauro et al., 2019; Halis et al., 2010; Vitale et al., 2009), our aim has been to provide a complete overview of the available evidence of psychiatric disorders across a number of diseases. Additionally, based on a literature search, we have summarized studies focused on the alterations in brain structure and resting-state connectivity in women with endometriosis. In addition to assessing the number of such studies, the number of patients included in them has also been taken into account in order to draw parallels between findings in endometriosis patients and alterations specific to patients with mental disorders like depression, anxiety and bipolar disorders, as well as those with chronic pain. We have sought to determine the extent to which it may be possible to postulate, based on these studies, whether the observed changes in brain structure or connectivity are specific to the *endometriosis brain* or if they just reflect coexisting mental comorbidities or pain conditions. Finally, based on our review of the literature, we discuss potential trajectories for future research as well as the gaps in our current understanding of endometriosis, and how new research strategies including up-to-date neuroimaging techniques and investigation of pain processing in the context of psychiatric comorbidities can help close those gaps.

2. Methods

For the analysis of mental disorder prevalence rates among patients

with endometriosis, the PubMed, PSYNDEX and Web of Science databases were searched for publications focusing on endometriosis in combination with confirmed diagnoses of mental disorders. To ensure the results' contemporaneity, the search was confined to papers published between January 2010 and June 2020. Studies were included in the analysis only if the mental disorder discussed therein had been diagnosed by trained clinicians, psychotherapists or psychiatrists according to the ICD (World Health Organization, 2020) or DSM (American Psychiatric Association, 2013) criteria and on the basis of clinical interviews or Structural Clinical Interviews for DSM (SCID) (First et al., 2016), or had been documented in clinical medical records and national health databases.

The search for mental disorders was performed using the following terms: *endometriosis* AND *diagnos** or *confirmed* combined with the mental disorders *depress**, *anxiety disorders, bipolar disorder, eating disorders, alcohol* and *drug dependence disorders, personality disorders, autism spectrum disorder, attention-deficit hyperactivity disorder* and *psychotic disorders*.

After identification of the data of potential interest, duplicates, publications with wrong topic and animal or qualitative studies (e.g. analyzing interview data or case reports), reviews and *meta*-analyses were discarded. The remaining studies were reviewed to ensure confirmed diagnoses of mental disorders in combination with endometriosis, with surveys pertaining to self-reporting and questionnaire-based psychological or psychiatric symptoms being excluded. Several studies met multiple exclusion criteria and were counted for each exclusion criterion. A few studies were found to involve several mental disorders, meeting the inclusion criteria. Articles that fulfilled the predefined inclusion criteria were included in the full-text analysis.

The database search for the neuroimaging data involved studies on voxel-based morphometry and functional resting-state connectivity in patients with endometriosis. To select publications on brain structure alterations in patients with endometriosis, the keywords *neuroimaging OR MRI brain* OR magnetic resonance imaging brain* OR brain imaging* AND endometriosis* were used to search the PubMed, PSYNDEX and Web of Science databases. Here too, we excluded duplicates, papers with wrong topic, animal studies, reviews and *meta*-analyses and considered the remaining studies for full-text analysis. To remove any possible bias introduced by the file-drawer effect, we also performed a search for unpublished studies, which constitute what is known as "gray literature", in Google Scholar using the above-mentioned key words (Tincani & Trevors, 2019). Given that no relevant papers could be identified, the probability of such a bias is estimated to be low.

3. Results

3.1. Major depression

The database search for major depression resulted in 168 articles, of which 47 were duplicates, 100 papers had the wrong topic, three were animal studies and 18 were reviews or *meta*-analyses. After excluding articles due to other exclusion criteria (see Fig. 1), nine studies remained for the full-text analysis. The screening process is depicted in Fig. 1.

3.2. Anxiety disorders

The search for papers on anxiety disorders yielded 31 publications, seven of which were duplicates, nine had a wrong topic and two were animal studies, leaving four studies for full-text analysis. Fig. 2 depicts the screening process.

3.3. Bipolar disorder

As depicted in Fig. 3, the database search for bipolar disorders and endometriosis resulted in eight papers. Three of them were duplicates and two were reviews, leaving three studies for the full-text analysis.

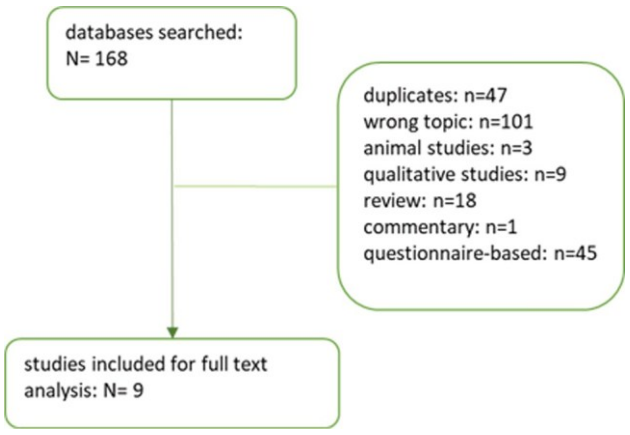

Fig. 1. Flow chart of the screening process during the systematic literature search concerning depressive disorders in endometriosis patients.

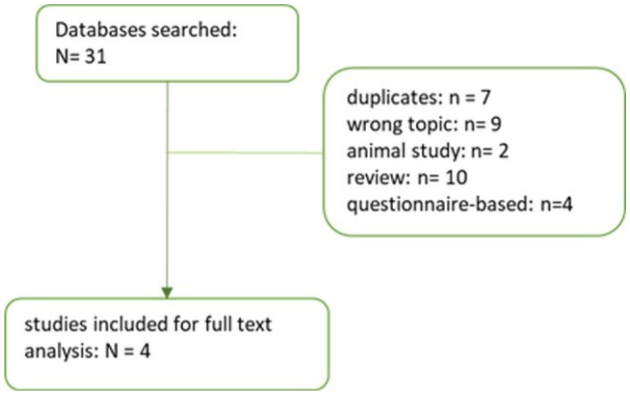

Fig. 2. Flow chart of the screening process during the systematic literature search concerning anxiety disorders in endometriosis patients.

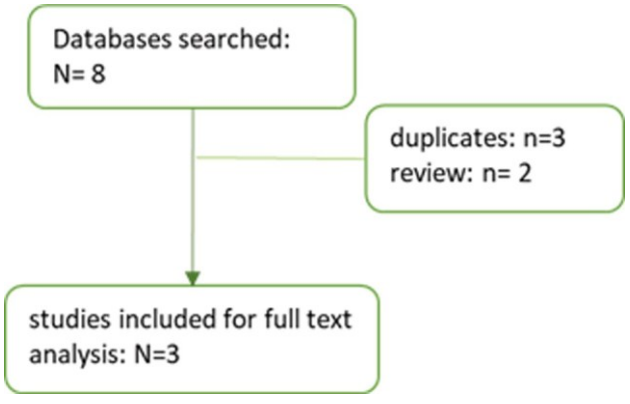

Fig. 3. Flow chart of the screening process during the systematic literature search concerning bipolar disorder in endometriosis patients.

3.4. Other mental disorders

The search for other mental disorders, except autism spectrum disorder, resulted only in the study by Gao et al. (2020), which was included in the analysis. Surprisingly, no article from the literature search could be considered for autism spectrum disorder despite Gao et al. (2020) reporting on that mental disorder. An overview of the screening process is summarized in Table 1.

Table 1
Screening process involving the search for further mental disorders in endometriosis patients.

Mental disorder	Hits in total	Dupli-cates	Wrong topic	Animal study	Qualitative study	Review	Question-naire based	Included in full text analysis
Eating disorders	4	2	2		1		1	1
Alcohol and dependence disorders	6		5	1				1
Personality disorders	6	1	2		1		2	1
Autism spectrum disorder	3	2	2			1		0
Attention deficit (Hyperactivity) disorder	3		1		1		1	1
Psychotic disorders	3		2		1	1		1

3.5. Study characteristics

Taken together, our search resulted in 232 papers, which were further screened for eligibility. Nine studies describing an association between endometriosis and comorbid mental disorders were available for the full-text analysis. A few studies, involving disparate methodological approaches, reported on several comorbid mental disorders in patients with endometriosis (e.g. Gao et al., 2020).

Three studies on comorbid mental disorders among patients with endometriosis were conducted in Europe (Cavaggioni et al., 2014; Gao et al., 2020; Warzecha et al., 2020), three in USA (Kumar et al., 2011; Smorgick et al., 2013; Taran et al., 2010), two in Taiwan (Chen et al., 2020; Chiang et al., 2018) and one in Israel (Greenbaum et al., 2019). Five studies analyzed data retrospectively (Chiang et al., 2018; Gao et al., 2020; Greenbaum et al., 2019; Smorgick et al., 2013; Taran et al., 2010) and four prospectively (Cavaggioni et al., 2014; Chen et al., 2020; Kumar et al., 2011; Warzecha et al., 2020). Six of the studies were cohort studies (Chen et al., 2020; Chiang et al., 2018; Gao et al., 2020; Greenbaum et al., 2019; Smorgick et al., 2013; Warzecha et al., 2020), while two were case-control studies (Cavaggioni et al., 2014; Taran et al., 2010) and one a cross-sectional study (Kumar et al., 2011). Five studies retrieved their data from local clinical records like hospitals or departments for gynaecology (Cavaggioni et al., 2014; Kumar et al., 2011; Smorgick et al., 2013; Taran et al., 2010; Warzecha et al., 2020) whereas four studies used data from national databases on health insurance and national registers (Chen et al., 2020; Chiang et al., 2018; Gao et al., 2020; Greenbaum et al., 2019). Endometriosis was confirmed by surgery in four studies (Cavaggioni et al., 2014; Kumar et al., 2011; Smorgick et al., 2013; Taran et al., 2010), of which two used verified diagnosis by histopathological examination (Cavaggioni et al., 2014; Taran et al., 2010). Two studies included endometriosis patients based on ultrasonography data (Chen et al., 2020; Warzecha et al., 2020) with the one by Warzecha et al. (2020) also relying on previous surgical confirmation. Another three studies relied on medical records without reporting further information (Chiang et al., 2018; Gao et al., 2020; Greenbaum et al., 2019). Five studies reported mental disorders based on medical records documented by trained physicians or psychiatrists (Chiang et al., 2018; Gao et al., 2020; Smorgick et al., 2013; Taran et al., 2010; Warzecha et al., 2020), one referred to the diagnosis made by board-certified psychiatrists (Chen et al., 2020) and two other studies used the SCID to assess comorbid mental disorders (Cavaggioni et al., 2014; Kumar et al., 2011). Six studies had a two-armed design, with four of them comparing endometriosis patients with women without endometriosis (Cavaggioni et al., 2014; Chen et al., 2020; Gao et al., 2020; Greenbaum et al., 2019) and, in two studies, also with patients with another condition, like uterus fibroids or CPP unrelated to endometriosis (Kumar et al., 2011; Taran et al., 2010). One study had a three-armed design comparing endometriosis and fibromyalgia patients with controls suffering from neither condition (Greenbaum et al., 2019).

Two studies reported on the extent of endometriosis according to the *revised American Society for Reproductive Medicine (rASRM) classification* (Smorgick et al., 2013; Warzecha et al., 2020), while one reported on the localization of endometriosis lesions (Cavaggioni et al., 2014) and one focused explicitly on adenomyosis (Taran et al., 2010), which is characterized by ectopic endometrial tissue within the uterine myometrium. The remaining studies did not report on specific localization and stages of the disease. In two studies, healthy controls were considered to not have endometriosis if they did not have symptoms, sonographic signs or history of surgery because of endometriosis (Cavaggioni et al., 2014; Greenbaum et al., 2019). In two other studies, endometriosis and adenomyosis were ruled out via diagnostic laparoscopy (Kumar et al., 2011; Taran et al., 2010). Only two studies reported on hormonal therapy for endometriosis (Chen et al., 2020; Smorgick et al., 2013).

3.6. Study population and mental disorder comorbidities

In total, the nine eligible studies included 268,734 patients with endometriosis and 1,639,072 women without endometriosis. Of these nine studies, the biggest ones, with 91% of the overall endometriosis population, were the cohort studies of Gao et al. (2020) and Chiang et al. (2018), which were based on national health-related databases.

Only one study described patients with endometriosis in more detail, discriminating between those with symptomatic (183 participants) and asymptomatic (56 participants) endometriosis (Warzecha et al., 2020). Out of the 1,639,072 control participants in all studies, additional information was available only with respect to 207 women, of whom 43 were reported to be healthy (Cavaggioni et al., 2014), unaffected by CPP, while 12 suffered from endometriosis-independent CPP (Kumar et al., 2011) and 152 had uterus fibroids (Taran et al., 2010). For the remaining control participants, no further details were available.

An overview of all analyzed studies is shown in Table 2.

As Fig. 4 shows, the range of selected mental disorder prevalence rates in endometriosis patients is quite broad according to the studies reviewed here (Cavaggioni et al., 2014; Gao et al., 2020; Greenbaum et al., 2019; Kumar et al., 2011; Smorgick et al., 2013; Taran et al., 2010; Warzecha et al., 2020). The major depressive disorder (MDD) rates demonstrate the widest distribution from 1.36% to 55.3% (Chiang et al., 2018; Taran et al., 2010) with the rates of anxiety disorders ranging from 3.7% to 29.7% (Cavaggioni et al., 2014; Kumar et al., 2011) and those of bipolar disorders from 0.85% to 44.44% (Chen et al., 2020; Kumar et al., 2011). Only one study reported on the prevalence of other mental disorders in patients with endometriosis, like eating disorders (2.96%), alcohol/drug dependence disorders (3.56%), personality disorders (4.86%), autism spectrum disorder (0.93%), attention-deficit disorder (4.07%) and non-affective psychotic disorders (0.87%) (Gao et al., 2020).

3.7. Neuroimaging and endometriosis

The database search with the afore-mentioned keywords (see section 2) resulted in 52 hits for neuroimaging and endometriosis (Fig. 5). Nine of them were duplicates, 28 had a wrong topic, three described animal studies, one was a qualitative study and seven were reviews, leaving three articles for the full-text analysis.

3.8. Neuroimaging study characteristics

Of the three neuroimaging studies involving patients with

Table 2
Overview of studies on comorbid mental disorders associated with endometriosis.

Article	Design	Experimental group	Control group	Results
Cavaggioni et al. (2014)	Two-armed, case-control study	37 patients with endometriosis[#]	43 healthy controls	Psychiatric disorders[*] were more prevalent in endometriosis patients (54%) than in healthy controls (18.6%), $p = 0.001$. Anxiety and mood disorders were more frequent in patients with pelvic pain (29.7% and 18.9%, respectively) than in the controls (7% and 9.3%, respectively), $p = 0.0342$.
Chen et al. (2020)	Two-armed, retrospective cohort study	17,832 patients with endometriosis[§]	17,832 controls without endometriosis[§]	The incidence rate of bipolar disorder in endometriosis patients was higher than in the controls (1.04 vs. 0.56 per 1000 person-years, respectively), adjusted HR = 2.34 (95% CI = 1.75–3.12). 27.4% patients with endometriosis received surgical treatment, 51.9% short-term and 48.1%- long-term hormonal therapy. No effect of therapy for endometriosis on the incidence of bipolar disorder.
Chiang et al. (2018)	One-armed, retrospective cohort study	229,617 patients with endometriosis[#]		Prevalence of depressive disorders was reported to be 1.36% in the study population.
Gao et al. (2020)	Two-armed, retrospective cohort study	14,114 patients with endometriosis[#]	839,696 controls without endometriosis	Higher prevalence of depressive disorders, anxiety disorders and bipolar disorders among patients with endometriosis (17.37%, 24.21% and 3.43%, respectively) as compared to the controls (9.14%, 12.91% and 1.91%, respectively)[**]. HRs before endometriosis diagnosis were for depressive disorders HR = 1.81 (95 %CI: 1.71–1.92), anxiety disorders HR = 1.94 (95 %CI: 1.84–2.04) and bipolar disorders HR = 1.64 (95 %CI: 1.44–1.86). HRs after endometriosis diagnosis were for depressive disorders HR = 1.89 (95 %CI: 1.78–2.01), anxiety disorders HR = 1.82 (95 %CI: 1.73–1.92) and bipolar disorders HR = 1.62 (95 %CI: 1.43–1.83).
Greenbaum et al. (2019)	Three-armed, retrospective cohort study	1) 6,647 patients with endometriosis[#]; 2) 25,425 patients with fibromyalgia[#]	781,571 controls without endometriosis or fibromyalgia	Prevalence of depression and/or anxiety was higher among patients with endometriosis alone (39.5%), fibromyalgia alone (62.3%) and endometriosis & fibromyalgia (63.1%) as compared to the controls (29.1%), $d = 0.72$.
Kumar et al. (2011)	Two-armed, cross-sectional study	27 patients with endometriosis[#]	12 patients with CPP of other origin	Compared to CPP patients, women with endometriosis suffered more often from bipolar disorder (0 vs. 44.44%, respectively, $p < 0.05$) and major depressive disorder or panic disorder (0 vs. 18.52%, respectively)[**], $p < 0.019$ for depressive disorder or bipolar disorder and $p < 0.05$ for bipolar disorder alone.
Smorgick et al. (2013)	One-armed, retrospective cross-sectional study	138 patients with endometriosis (hormonal therapy n = 136)		48% of patients with endometriosis had depression and/or anxiety. Other pain conditions[***] increased the likelihood of mood disorders in endometriosis patients, OR = 2.1 (95 %CI: 1.4–3.2).
Taran et al. (2010)	Two-armed, retrospective case-control study	76 patients with adenomyosis uteri (hormonal therapy n = 55)	152 patients with uterine fibroids (hormonal therapy n = 81)	Patients with adenomyosis had more often depression (55.3%) as compared to the controls (22.2%), OR = 3.5 (95 %CI: 1.9–6.2), $p < 0.001$.
Warzecha et al. (2020)	One-armed, cohort study	a) Patients with endometriosis N = 246 (hormonal therapy n = 91[**]); symptomatic, n = 183; b) asymptomatic, n = 56.		15.1% of patients with endometriosis had a depressive disorder. Patients with endometriosis had a higher likelihood to develop a depressive disorder if they suffered from CPP, OR = 3.8 (95 %CI: 1.2–12.8) or dyschezia, OR = 7.7 (95% CI = 1.4–42.3).

Notes: CPP = chronic pelvic pain, CI = confidence interval, HR = hazard ratio, OR = odds ratio.
[$]all participants received short- or long-term hormonal therapy.
[*] psychotic disorder not otherwise specified, dysthymic disorder, major depressive disorder, depressive disorder not otherwise specified, bipolar II disorder, generalized anxiety disorder, panic disorder without agoraphobia, specific phobia, social phobia, obsessive–compulsive disorder, anxiety disorder not otherwise specified, eating disorder not otherwise specified, undifferentiated somatoform disorder.
[**] values calculated to improve comparability, based on the reported data.
[***] interstitial cystitis, irritable bowel syndrome, fibromyalgia, chronic headaches, chronic low back pain, temporomandibular joint disease, vulvodynia, and chronic fatigue syndrome.
[#] no information on hormonal therapy or inclusion of patients with current hormonal therapy.

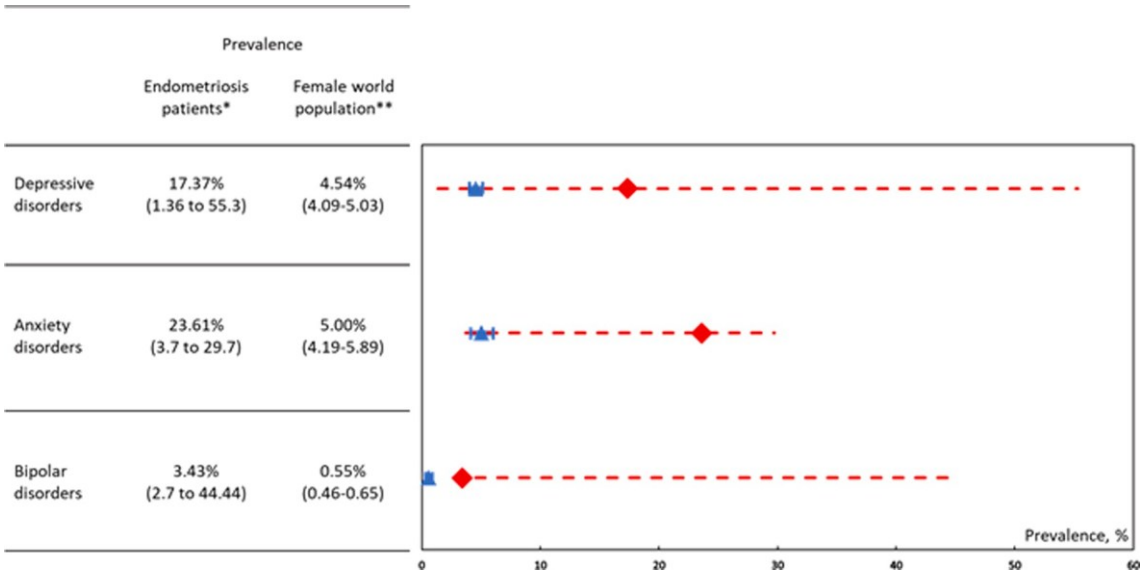

Fig. 4. Prevalence of selected mental disorders among endometriosis patients in comparison to the female world population. Notes*: *the prevalence of the corresponding mental disorders in endometriosis patients was calculated as the median with the range (provided in the parentheses) of the prevalence rates extracted from reviewed original articles (*Cavaggioni et al., 2014; Chiang et al., 2018; Gao et al., 2020; Greenbaum et al., 2019; Kumar et al., 2011; Smorgick et al., 2013; Taran et al., 2010; Warzecha et al., 2020*) and depicted as red diamond with red dashed line, corresponding to the range. **The prevalence of corresponding mental disorders in the female world population (*The Institute for Health Metrics and Evaluation, 2019*) expressed as the mean with 95% confidence interval in the parentheses and depicted as blue triangle with blue solid line, corresponding to the 95% confidence interval.* (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

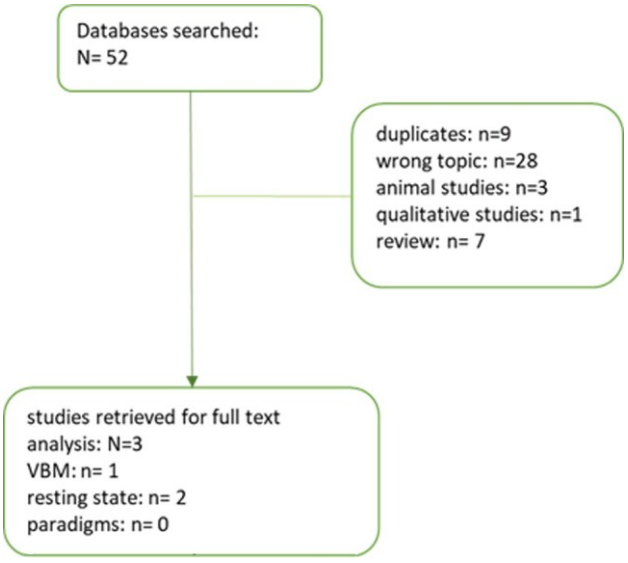

Fig. 5. Flow chart of the screening process during the systematic literature search concerning neuroimaging in endometriosis patients. Notes: *VBM = voxel-based morphometry*.

endometriosis (Table 3), two were by As-sanie et al. (2012; 2016), both of which were observational, two-armed case-control studies on voxel-based brain morphometry (As-sanie et al., 2012) and resting-state neuroimaging (As-Sanie et al., 2016). The study on voxel-based morphometry and endometriosis included 17 women with symptomatic endometriosis, 13 with asymptomatic endometriosis, 6 with CPP of other origin and 26 healthy controls. The trial on functional resting-state connectivity included overlapping participants with two more women with CPP and 11 more healthy controls. Endometriosis was surgically confirmed in all patients and the disease stage was determined according to the *rASRM*. Healthy women, who did not have chronic pain or dysmenorrhea, were used as comparators in both studies.

The third trial was a prospective, interventional two-armed randomized controlled study (Beissner et al., 2018), in which 67 patients with severe endometriosis-associated pain were randomly allocated to intervention (35 patients) or waitlist control (32 patients) groups. Resting-state functional magnetic resonance imaging (fMRI) was used to assess brain connectivity of these patients at baseline, after 3 months of therapy, and after 6 months. The intervention included psychotherapy (with elements of mindfulness-based psychotherapy, hypnotherapy, problem-solving therapy, and cognitive–behavioral therapy) with somatosensory stimulation by means of traditional Chinese techniques (acupuncture, moxibustion (heat), and cupping). The stage of endometriosis was also reported according to the *rASRM*.

3.9. Results of neuroimaging studies

Compared to healthy controls, women with symptomatic endometriosis showed decreased gray matter volume in the left thalamus, the left middle frontal gyrus (MFG), the left and right midcingulate cortices (MCC), the right putamen and the right insula and increased gray matter volume in the left amygdala (As-sanie et al., 2012; Fig. 6). In contrast, asymptomatic endometriosis patients had increased gray matter volume in the right periaqueductal gray (PAG), the right inferior frontal gyrus (IFG) and the right MFG and gray matter volume decreases in the right inferior temporal gyrus (ITG) as compared to healthy controls (Fig. 6). Additionally, symptomatic endometriosis patients demonstrated an increased resting-state connectivity between the anterior insula and the left dorsomedial prefrontal cortex (PFC), the left mPFC and the left occipital cortex compared to their healthy counterparts, whereas asymptomatic patients did not differ in resting-state connectivity from the healthy controls (As-Sanie et al., 2016; Fig. 7). Patients with endometriosis-independent CPP showed a gray matter volume decrease in the left thalamus as compared to healthy controls.

The study by Beissner et al. (2018) demonstrated a reduction in the number of symptoms in women with endometriosis following psychotherapy with somatosensory stimulation. In comparison with wait-list controls, treated patients showed improvements with respect to pelvic

Table 3
Overview of studies on neuroimaging in endometriosis patients.

Article	Design	Experimental group	Control group	Results
As-Sanie et al. (2016)	Observational two-armed case-control study	36 patients with 1) symptomatic endometriosis n = 17 (hormonal therapy n = 10);2) asymptomatic endometriosis n = 13 (hormonal therapy n = 4);3) CPP without endometriosis n = 6 (hormonal therapy n = 4).	24 healthy controls were age-matched divided in three overlapping groups: for arm 1n = 14; for arm 2n = 12; and for arm 3n = 11*	Increased resting-state brain connectivity between the anterior insula and the mPFC & occipital cortices in patients with symptomatic endometriosis as compared to healthy controls. No differences in resting-state connectivity could be detected in patients with asymptomatic endometriosis as compared to controls or CPP.
As-Sanie et al. (2012):	Observational two-armed case-control study	38 patients with1) symptomatic endometriosis n = 17 (hormonal therapy n = 10);2) asymptomatic endometriosis n = 15 (hormonal therapy n = 4);3) CPP and without endometriosis n = 6 (hormonal therapy n = 4).	26 healthy controls (hormonal therapy n = 17)	Compared to controls:1) Decrease of gray matter volume in left thalamus, left MFG, bilateral MCC, right putamen, right insula cortex and increase in left amygdala in symptomatic endometriosis patients.2) Increase of gray matter volume in right PAG, right IFG, right MFG and decrease in right ITG in asymptomatic endometriosis patients.3) Decrease of gray matter volume in left thalamus in patients with endometriosis-independent CPP.
Beissner et al. (2018)	Interventional two-armed randomized study	35 patients with symptomatic endometriosis with intervention (psychotherapy and somatosensory stimulation)*	32 patients with symptomatic endometriosis without study intervention*	Psychotherapy reduced trait anxiety, leading to a decrease of connectivity between anterior hippocampus and primary and secondary somatosensory cortex, SMG, posterior MCC, right FIC, and temporal pole.

Notes: CPP = chronic pelvic pain. mPFC = medial prefrontal cortex. MFG = middle frontal gyrus. MCC = midcingulate cortex. PAG = periaqueductal gray. IFG = inferior frontal gyrus. ITG = inferior temporal gyrus. SMG = supramarginal gyrus. FIC = frontoinsular cortex.
* no information on hormonal therapy or inclusion of patients with current hormonal therapy.

pain, painful defecation, symptoms of anxiety and depression based on the questionnaires and physical and mental quality of life after three months. These changes were associated with a decrease in the connectivity between the anterior hippocampus and both the primary and the right secondary somatosensory cortices (SSC), the supramarginal gyrus (SMG), the posterior MCC, the right frontoinsular cortex (FIC), the temporal pole, the anterior insula and the mPFC. Regression analysis showed that the reduction in connectivity had predicted the therapy-induced improvement in patients' anxiety.

4. Discussion

Patients with symptomatic endometriosis often suffer from the condition and, as a result, poor quality of life for years before being diagnosed with endometriosis (Zondervan et al., 2020). The negative effects of the disorder accumulate further after the diagnosis with frequent symptom recurrence following (repeated) surgery. Not surprisingly, women affected by endometriosis are susceptible to a number of psychosocial risk factors (and vice versa), which lead to the development of mental disorders across the patients' lifespan. Based on the nine studies included in this review, we can conclude that, in women with endometriosis, there is a high prevalence of depression and anxiety disorders, bipolar disorder (Cavaggioni et al., 2014; Chen et al., 2020; Greenbaum et al., 2019; Kumar et al., 2011), and, in some cases, increased alcohol/drug dependence (3.56% in endometriosis patients (Gao et al., 2020) vs. 1.25% (95 %CI: 1.13–1.4) as well as attention-deficit hyperactivity disorder (4.07% in endometriosis patients (Gao et al., 2020) vs. 0.62% (95 %CI: 0.45–0.83) in the female world population (The Institute for Health Metrics and Evaluation, 2019). In women suffering from symptomatic endometriosis, a number of factors contribute to the increased prevalence of psychiatric problems with the most important of them being pain and additional somatic comorbidities, like fibromyalgia, interstitial cystitis, migraine, chronic fatigue syndrome that frequently co-occur with endometriosis (Boneva et al., 2019; Greenbaum et al., 2019). Hormonal treatments, inflammation or genetic predisposition are also addressed here as they seem to play an important role in the development of mental disorders. Furthermore, we have summarized the available data on the alterations of brain structure and functional connectivity seen in patients with endometriosis.

4.1. Comorbidities among patients with endometriosis

Despite more than 50 reports on the possible association of endometriosis with depressive and anxiety symptoms, only nine studies were found to involve objectively confirmed diagnoses of mental disorder and, therefore, were included in this review. As expected, the prevalence of confirmed depression or anxiety disorders as a comorbidity of endometriosis, with a median of 17.37% and 23.61%, respectively, was found to be lower than that derived from studies based only on self-reported outcomes (about 40–50% and 55%, respectively) (Donatti et al., 2017; Ma´rki et al., 2017; Roomaney et al., 2020). However, the frequency of mental disorders (even after excluding the results based only on self-reported assessments) considerably exceeded the prevalence of these conditions both in the healthy controls of the reviewed studies and the general female population (Fig. 4). The prevalence rate of bipolar disorder was roughly six times higher than in the female world population, and that of depression and anxiety more than twice as high. Given a high coincidence of mental disorders, like depressive and anxiety disorder, of about 38–63%, (Wittchen, 2002), we can assume that at least one-third of endometriosis patients seem to have a mental disorder and, therefore, require professional psychiatric or psychotherapeutic assistance.

Undoubtedly, the prevalence of mental disorders is influenced by specific cultural and socio-economic factors, which can also be responsible for the large variation in the prevalence of mental disorders between different national populations of endometriosis patients. For instance, Taiwanese patients with endometriosis showed the lowest

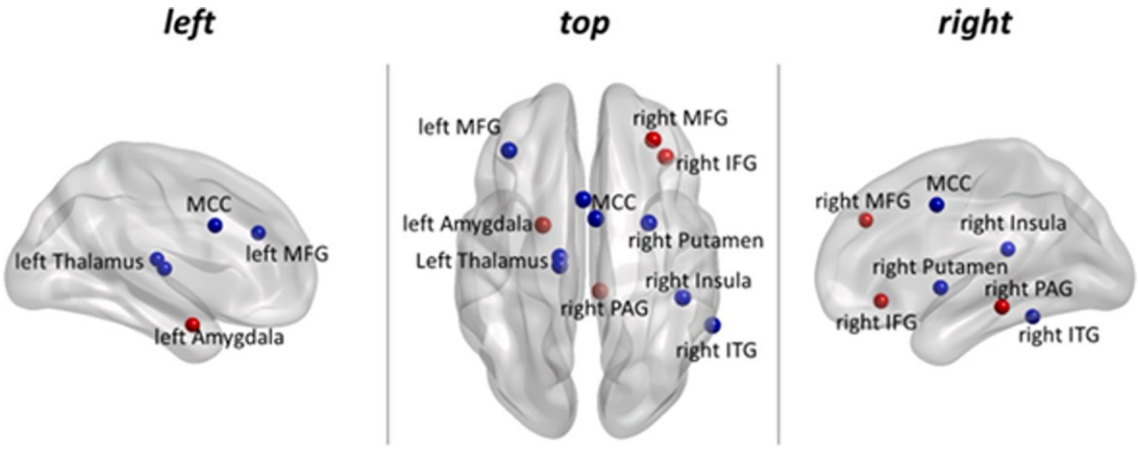

Fig. 6. Alterations in brain morphology in patients with symptomatic and asymptomatic endometriosis compared to healthy controls. Notes: *left, top and right views of the examined brain areas. Red indicates increased gray matter volume; blue indicates decreased gray matter volume. MCC: (bilateral) midcingulate cortex; MFG: (left) middle frontal gyrus; PAG: periaqueductal gray; IFG: inferior frontal gyrus; ITG: inferior temporal gyrus. Modified from* As-sanie et al., 2012. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

prevalence of depression (1.36%) with the prevalence of MDD in general being quite low (1.20%) in Taiwan (Chiang et al., 2018; Liao et al., 2012). It has been suggested that the structured diagnostic interviews designed in the West fail to elicit information regarding the symptoms of depression from Asian patients, who tend to repress their emotions owing to what is often referred to as "oriental stoicism". This culturally determined "response bias" likely skews such instruments toward a lower estimate of the prevalence of depressive disorders among Asian populations (Liao et al., 2012). Using screening instruments particularly adapted to Taiwanese populations, recent studies have found a much higher prevalence of depression in Taiwanese adults (above 10%) (Tai et al., 2014). Contrary to the study by Chiang et al. (2018), the one by Greenbaum et al. (2019) found an extremely high prevalence of depression or anxiety (29.1% depression and/or anxiety) in Israel. In this study, the presence of endometriosis was found to increase the prevalence of mental disorders up to 39.5%, and even further (up to 63%) if fibromyalgia co-occurred with endometriosis. However, women with fibromyalgia without endometriosis also demonstrated similar rates of depression and/or anxiety (up to 62.3%). It can be assumed, therefore, that specific cultural factors, somatic comorbidities or other pain conditions co-occurring with endometriosis are linked to higher rates of depression or anxiety. The study by Taran et al. (2010) found that more than one-half of patients with adenomyosis (with and without other manifestations of endometriosis) had a history of depression compared to approximately one-quarter of those with uterus fibroids (52.6% vs. 22.2%), and were also more likely to be susceptible to infertility and pelvic pain. Finally, Gao et al. (2020) demonstrated that, after adjustment for birth characteristics and education, women with endometriosis had a higher risk of being subsequently diagnosed not only with depressive or anxiety disorders but also with alcohol/drug dependence and attention-deficit hyperactivity disorder.

Interestingly, it is not only the comorbidity but also the experience of pain itself that is thought to be associated with an increased prevalence of mental disorders. According to a recent *meta*-analysis (Gambadauro et al., 2019), the link between endometriosis and depressive symptoms is largely determined by chronic pain, with no significant difference in prevalence of depression being found between women with pelvic pain and endometriosis and those with pelvic pain but without endometriosis (de Carvalho et al., 2015; Warzecha et al., 2020). A study by Warzecha et al. (2020) demonstrated that it is not only the severity of pain but also its type that can influence the prevalence of mental disorders. While patients with chronic pelvic pain and dyschezia are more likely to develop a depressive disorder, conditions such as dysuria, dyspareunia or dysmenorrhea do not seem to increase the prevalence of mental comorbidities. Also, asymptomatic patients with endometriosis have been found to be much less prone to depressive or anxiety disorders than

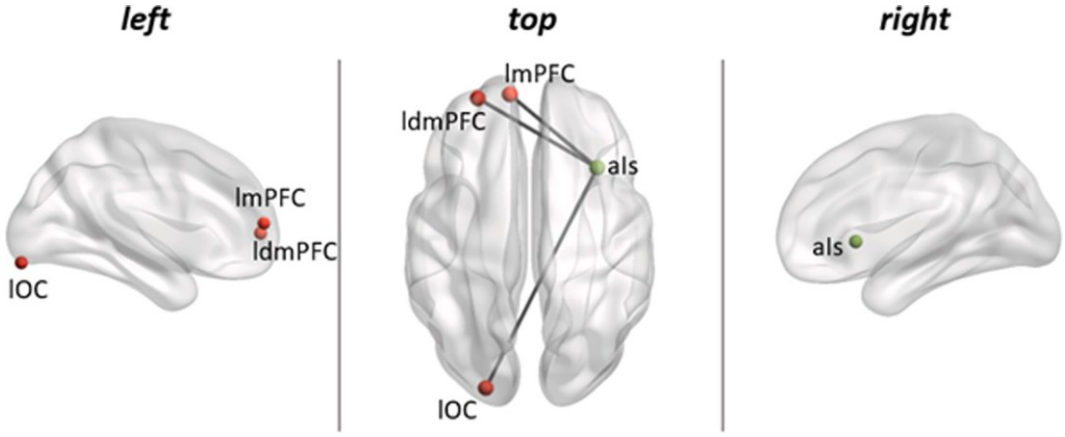

Fig. 7. Changes in resting-state functional connectivity in patients with symptomatic endometriosis compared to healthy controls. Notes. *Left, top and right views of the examined brain areas. Red indicates increased connectivity; green indicates the seed region. aIs: anterior insular seed/region of interest; lOC: left occipital cortex; lmPFC: left medial prefrontal cortex; ldmPFC: left dorsomedial prefrontal cortex. Modified from* As-sanie et al. 2016. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

women with pain symptoms (As-sanie et al., 2012; Cavaggioni et al., 2014; Facchin et al., 2015; Gambassi, 2009; Pope et al., 2015). However, the data on the prevalence of mental disorders in asymptomatic patients with endometriosis are limited to the studies using self-reporting outcomes and, therefore, need to be reproduced using objective diagnostic methods. It is not yet possible to ascertain the extent to which pain increases the prevalence of psychiatric disorders in women diagnosed with endometriosis; more studies are needed therefore to address this question. It may not only be pain alone but individual and context-specific vulnerabilities (Gambadauro et al., 2019), including pain-coping strategies (Donatti et al., 2017) and hormonal treatment, may also contribute to the development or aggravation of mood disorders. For instance, As-sanie et al. (2012) found increased PAG gray matter volume in women with asymptomatic endometriosis compared to healthy controls. It is possible that those alterations were either related to initially high pain thresholds (e.g. lower predisposition to the development of pain sensation) of the affected patients, explaining the asymptomatic course of the disease, or were caused secondarily by the pain processing system adapting to the noxious stimuli (As-sanie et al., 2012). It must be noted that depression is a frequent side effect of hormone therapy, which is more of a rule than an exception in endometriosis, typically with progestogen-only methods as first-line therapy (Gambassi, 2009; Gao et al., 2020; Pope et al., 2015; Quaas et al., 2015). Thus, we maintain that long-term exposure to hormonal treatment is likely to contribute to what may be termed the *endometriosis brain*. However, given that the treatment reduces the pain, it is associated with more positive than negative effects. Thus, because hormone therapy alleviates pain, it can be seen as a factor that helps reduce the load of psychiatric comorbidities. Only four out of the nine studies analyzed in the present review reported on hormone therapy of the participants (see Table 2), with no association being detected between the treatment and the development of a bipolar disorder (Chen et al., 2020; Kumar et al., 2011). Additionally, no influence of the duration of hormonal treatment on the incidence of depressive disorders was observed (Warzecha et al., 2020).

One intriguing observation is that the prevalence of bipolar disorder in women with endometriosis is much higher than in the general population. However, the data in this regard are quite wide-ranging, reaching more than 40% in the study by Kumar et al. (2011), whereas only 0.55% of the unselected female world population is affected by the illness (The Institute for Health Metrics and Evaluation, 2019, Fig. 4). Despite being repeatedly indicated by different studies (Chen et al., 2020; Dinsdale & Crespi, 2017; Kumar et al., 2011; Pope et al., 2015), the connection between bipolar disorder and endometriosis remains unclear. Unlike depression or anxiety, pain seems not to play a leading role in bipolar disorder, the condition not being found to be more prevalent in patients with other chronic pain conditions (Kumar et al., 2011). However, the hormonal effects (e.g. fluctuation of circulating sex hormones in women, especially in relation to the menstrual cycle) seem to play a role. Generally, surgical menopause (e.g. after bilateral oophorectomy) has a negative impact on future psychosexual as well as cognitive and mental health (Hickey et al., 2010). Women with hysterectomy seem to have an increased risk of bipolar disorder, especially if oophorectomy is simultaneously performed or endometriosis is present (Shen et al., 2019). According to some reports, women with bipolar disorder have high rates of premenstrual worsening of mood (Blehar et al., 1998), which has also been observed in women suffering from endometriosis (e.g. Tanaka et al., 2016). Also, in some cases (due to extreme mood swings), endometriosis with severe menstrual symptoms can mimic the symptoms of bipolar disorder, particularly the so-called rapid cycling bipolar disorder. The premenstrual symptoms, observed in patients with both endometriosis and bipolar disorder, may indicate common pathogenetic mechanisms like altered susceptibility to menstrual cycle-dependent hormonal fluctuation, resulting in menstrual distress. However, this issue is yet to be thoroughly investigated. Dysregulations within the female oxytocin system, which are observed in women with endometriosis, may mirror potential malfunction of the hypothalamic-pituitary–gonadal axis, increasing the risk of bipolar disorder (Dinsdale & Crespi, 2017). This assumption, however, remains controversial and requires further investigation (Rutigliano et al., 2016). Other factors that appear to play an important role in the development of psychiatric comorbidities in patients with endometriosis are inflammation and genetic predisposition. Several *meta*-analyses have shown increased levels of inflammatory markers in patients with bipolar disorder, including soluble interleukin (IL)-2 receptor (sIL-2R), sIL-6R, TNF-alpha, soluble TNF receptor-1, and IL-4 (Modabbernia et al., 2013; Rowland et al., 2018). Based on that, it has been suggested that inflammation and oxidative stress are connected in complex ways to impaired neuroplasticity and, thus, to the development of bipolar disorder (Wollenhaupt-Aguiar et al., 2021) and a number of psychiatric disorders including depression (Beurel et al., 2013) and psychosis (Müller et al., 2015). At least some of these proinflammatory changes have also been observed in patients with endometriosis (Zondervan et al., 2020). In addition, various genetic confounders may account for the frequent comorbidity between mental disorders and endometriosis. Gao et al. (2020), for instance, have found female siblings of patients with endometriosis to be at an increased risk of developing mental disorders, even if they themselves do not suffer from endometriosis. In line with that, a recent study has suggested a common genetic etiology linked to gastric mucosa abnormalities in patients with endometriosis and depression (Adewuyi et al., 2021). According to this study (and contrary to previous reports), a somewhat similar genetic etiology, but not pain (or chronic pain), is likely to be the key determinant of the association between endometriosis and depression (Adewuyi et al., 2021). Similar analyses with respect to genetic factors influencing the prevalence of bipolar depression or other psychiatric conditions in women with endometriosis would be useful.

4.2. Complex reciprocal relationship between mental problems and endometriosis

Collectively, the studies analyzed here highlight a complex and sometimes reciprocal relationship between endometriosis and mental health. Comorbid mental disorders in patients with endometriosis are usually prognostically unfavorable as they may aggravate symptoms of the disease, affect quality of life and increase the therapy costs (Mirkin et al., 2007; Valderas et al., 2009). In women with endometriosis, pain is thought to play a crucial role in the development of mental problems like depression or anxiety. On the other hand, psychiatric history also seems to be a risk factor for the development of endometriosis. For instance, women with a history of mental disorder (e.g. psychosis, depressive disorder, anxiety, eating or personality disorder, or attention-deficit hyperactivity disorder) are more likely to be diagnosed with endometriosis (Gao et al., 2020). Altered pain perception, which is frequently observed in psychiatric disorders (in particular, in anxiety disorder or depression) (Gorczyca et al., 2013; Thompson et al., 2016), likely contributes to earlier manifestation and diagnosis of endometriosis via symptoms of pain. Also, genetically-determined hormonal imbalance, *central sensitization* due to inflammation or early life stress, changes in various biological pathways and neurotransmitters or oxytocin levels may increase the susceptibility not only to endometriosis, but also to mental disorders (Dinsdale & Crespi, 2017; Gambassi, 2009). In addition, in women with affective disorder, changes in the affective state can be provoked by hormonal fluctuations during the menstrual cycle (Albert & Newhouse, 2019), indicating an elevated susceptibility to menstrual cycle-dependent hormonal fluctuations. To what degree it may be the case in patients with endometriosis, remains to be determined.

All in all, pain, infertility, the presence of somatic comorbidities, shared genetic vulnerability or altered immunological response as well as commonly prescribed hormonal therapies can contribute to the development of psychiatric disorders in women with endometriosis.

While it is unclear whether psychiatric disorders represent the causes or the consequences of endometriosis, it is highly likely that they can be both causes and consequences depending on individual circumstances.

4.3. Limitations of the analyzed studies on endometriosis and comorbidities

Our systematic review of the literature helped to identify several limitations in the studies involving the comorbidity between mental disorders and endometriosis. All the analyzed studies suffer from, among other things, a lack of effective operationalization, including the differentiation between symptomatic or asymptomatic endometriosis and the stage of the disease. None of the studies involved a systematic investigation of asymptomatic endometriosis in contrast to the symptomatic disease course. Since the majority of the studies were retrospective cohort trials, based on medical databases, the diagnostic approaches to endometriosis showed a considerable variation. Despite laparoscopy with the histological confirmation of endometriosis being the diagnostic gold standard, some studies also included patients who had been diagnosed by other methods, e.g. ultrasound (e.g. Warzecha et al., 2020). Furthermore, no detailed information was made available with respect to the mental disorders investigated in combination with the related symptoms. For instance, anxiety disorders, which comprise a variety of symptoms according to ICD (World Health Organization, 2020), were often not differentiated (e.g. Gao et al., 2020). Also, the control groups used as a reference for comparison with endometriosis patients varied from healthy controls to patients with chronic pain of other origin or uterus fibroids (e.g. Cavaggioni et al., 2014; Gao et al., 2020; Kumar et al., 2011; Taran et al., 2010). Additionally, there was often no information about the onset of mental disorders and endometriosis, with only Gao et al. (2020) including data on a months-long lag between the diagnoses of endometriosis and mental disorders. This heterogeneity likely influenced the results, restricting the establishment of a causal relationship between endometriosis and comorbid mental disorders.

4.4. Pain processing networks and endometriosis

Given the role of *central sensitization* in the development of chronic pain, it is surprising that, to date, only three studies have (indirectly) addressed this issue using brain neuroimaging techniques in patients with endometriosis. Chronic pain is known to be associated with alterations in brain structure and connectivity (Alshelh et al., 2018; Tatu et al., 2018). In women with symptomatic endometriosis (compared to healthy controls), As-sanie et al. (2012) have observed gray matter volume reduction in the thalamus, the cingulate, the insula, the putamen, the mPFC, the hippocampus and the somatosensory cortices, regions that are involved both in the affective and sensory aspects of pain processing (Apkarian et al., 2009; Gambassi, 2009). The lateral thalamus and the primary and secondary somatosensory cortices in particular are responsible for the sensory aspects of pain (constituting the so-called primary sensory pathway), processing acute pain stimuli like duration, intensity and pain localization. On the other hand, the medial thalamus and the mPFC (along with the amygdala, the PAG and the hypothalamus) are thought to be key brain areas comprising the affective pathway, which likely modulates the nociceptive processing of pain (Apkarian et al., 2009). The insular cortices seem to be involved in both (the affective and the sensory) pathways (Apkarian et al., 2009; Gambassi, 2009). In this regard, the increased amygdala volume in symptomatic endometriosis patients is noteworthy (As-sanie et al., 2012; Fig. 6) given that, as one of the central structures of the affective pain processing pathway, the amygdala modulates the emotional aspects of pain perception, emotional learning and memory (Davis & Whalen, 2001; Quirk & Beer, 2006) as well as fear and anxiety (Davis, 1992). Similarly, the anterior insula and the anterior cingulate and somatosensory cortices are thought to mediate perception of sensations from inside the body (interoceptive awareness) in the context of emotional processing (Khalsa et al., 2009). The mPFC, on the other hand, receives ascending, nociceptive and interoceptive inputs and also exerts important top-down control of pain sensation, evaluation and categorization of interoceptive stimuli (Kummer et al., 2020). Thus, a disturbance in the regulatory function of the PFC with respect to the amygdala or the ACC can contribute to *central sensitization* and, consequently, to the development of inflammatory or neuropathic pain (Kummer et al., 2020).

In symptomatic endometriosis patients (compared to their age-matched, pain-free counterparts), an enhanced connectivity has been observed between the anterior insula and the mPFC, the connectivity strength correlating with the severity of pain, anxiety and depression (As-Sanie et al., 2016), underscoring, once again, the role of negative emotions in the development of chronic pain. Other neuroimaging studies in humans have demonstrated how the anterior insula and the mPFC can be linked to the subjective perception of pain and its modulation based on the context of pain experience. Moreover, even in healthy controls, the anterior insula-mPFC connectivity has been found to be enhanced during the experience of uncontrollable pain (Bra¨scher et al., 2016). As patients suffering from endometriosis often report feeling a loss of control, perceiving the pain as unpredictable (Rush & Misajon, 2018), the alteration in their anterior insula-mPFC connectivity may no longer be only context-dependent but also permanently altered.

In patients with endometriosis, Beissner et al. (2018) have shown the role of the connectivity between the anterior hippocampus (the region involved in the processing of anxiety, stress regulation and affective (autobiographic) memory (LaBar & Cabeza, 2006; Zeidman & Maguire, 2016) and the regions forming the viscerosensory pathways. Following psychotherapy and acupuncture and the consequent reduction in pain, a reduced connectivity has been seen between the anterior hippocampus and the somatosensory cortex, the anterior insula/temporal pole and the mPFC (Beissner et al., 2018). In addition, a reduced resting-state connectivity between this network and the right anterolateral hippocampus has been found to be predicted by therapy-induced reductions in trait anxiety (Beissner et al., 2018) and not by pain scores. Collectively, these neuroimaging studies underscore the role of the mPFC, the anterior insula, the somatosensory cortex and the anterior hippocampus/amygdala/temporal pole in the perception and regulation of pain in patients suffering from endometriosis. Highlighting the role of negative emotions, such as depression or anxiety, in the pain experience of these patients, the results show why pain management alone is often not sufficient to mitigate the experience of pain in endometriosis.

4.5. Not only pain but also emotion, cognition, self-regulation and reward

The regions associated with endometriosis play a role not only in pain processing but also in a large number of disparate processes including the regulation of emotions (e.g. insula, mPFC/ACC, hippocampus, amygdala), cognition (e.g. mPFC, hippocampus, insula), motivation (e.g. mPFC), social reward system (e.g. basal ganglia, hippocampus, thalamus, amygdala), self-regulation and social normative behavior (e.g. anterior insula, mPFC) (Bellucci et al., 2018; Etkin et al., 2011; Felix-Ortiz et al., 2016; Gu et al., 2019; LaBar & Cabeza, 2006; Sesack & Grace, 2010; Stein, 2015; Van Overwalle, 2009; Zeidman & Maguire, 2016). They have also been found to be linked to a number of psychiatric conditions. Studies in MDD have identified functional as well as structural abnormalities in the mPFC (particularly in the subgenual cingulate cortex), the hippocampus and the amygdala (Gray et al., 2020). The amygdala and the mPFC play a crucial role in the regulation of fear and anxiety (Davis, 1992), and both regions have been shown to be altered in anxiety disorders (Etkin et al., 2009; Stein, 2015). Alterations in the gray matter volume of the amygdala, the insula and the mPFC/cingulate cortex have been demonstrated in patients with depression and bipolar disorders (Gray et al., 2020; Usher et al., 2010; Wise et al., 2017). Given the substantial overlap between brain regions

involved in a number of psychiatric conditions (e.g. depression, anxiety and bipolar disorders) and chronic pain, it is hardly surprising that both psychiatric and chronic neuropathic pain conditions are frequently linked to anxiety, depressive symptoms and reduced sociability (Kummer et al., 2020). As the mPFC is involved in aversive learning, memory as well as top-down control of pain sensation, the region is thought to serve as a hub for the development of chronic pain-related mental comorbidities such as depression and anxiety (Kummer et al., 2020). It is conceivable, therefore, that the clinical manifestation of depression or anxiety disorder or any other psychiatric condition can potentially affect the treatment of endometriosis (e.g. intercourse with pain relief and improvement of quality of life). All of this underscores the role of emotions (e.g. anxiety or sadness) in the development of endometriosis-specific symptoms in patients, explaining why endometriosis is so frequently associated with psychiatric comorbidities, and how negative emotions, perception of pain or psychiatric comorbidity may contribute to *central sensitization.*

4.6. Limitations of the analyzed neuroimaging studies on endometriosis

The neuroimaging studies on endometriosis that have been analyzed here suffer from several noteworthy drawbacks. Only two small studies compare brain morphology and resting-state connectivity between women with endometriosis and healthy controls. Additionally, they include the same cohort of only 17 patients with symptomatic endometriosis and a comparable number of asymptomatic patients (As-sanie et al., 2012; As-Sanie et al., 2016). No comparison with healthy controls is included in the study by Beissner et al. (2018). Thus, of the three neuroimaging studies involving patients with endometriosis, two are published by one research group, that of As-sanie et al. (2012; 2016). Given the limited sample sizes, the observed changes in brain structure and connectivity may have been influenced by individual characteristics of the study participants and, therefore, may not be generalizable to the population of women with endometriosis as a whole. For instance, the hormone therapy, which was used by half of the participants with symptomatic endometriosis in the studies by As-Sanie et al. (As-sanie et al., 2012; As-Sanie et al., 2016), may also have influenced the brain morphometry and function. However, it is unlikely that the described changes (As-sanie et al., 2012; As-Sanie et al., 2016) can be explained solely in terms of the influence of hormones, since the proportion of women receiving hormone therapy was similar between the control group and patients with symptomatic endometriosis (As-sanie et al., 2012; As-Sanie et al., 2016). Moreover, the alterations observed in these studies do not completely overlap with brain changes associated with hormone therapies (Toffoletto et al., 2014). Besides, Beissner et al. (2018), who demonstrate connectivity alterations during psychotherapeutic intervention with somatosensory stimulation in endometriosis patients, included only women without hormone therapy. While they afford important insight, the results of these three studies need to be treated with caution until they are replicated in larger patient collectives. To control for the disorder's heterogeneity, the neuroimaging data need to be correlated with the clinical data and the objectively assessed psychopathological comorbidities in larger patient groups. Finally, as most neuroimaging studies on chronic pain and mental disorders do not control for possible gender/sex effects (Gray et al., 2020; Kaiser et al., 2015), any indirect comparison of structural and connectivity alterations between women with endometriosis and patients with chronic pain or mood disorders is likely to be biased. Therefore, it is difficult to conclude if brain changes in patients with depression and chronic pain are gender-specific. Several *meta*-analyses on this issue show contradictory results (Iwabuchi et al., 2015; Kambeitz et al., 2017; Wise et al., 2017).

4.7. Research goal

The frequent recurrence of symptoms following (repeated) surgical therapy is one of the most daunting challenges associated with the treatment of endometriosis. Alongside adjuvant hormone treatment aimed at the prevention of disease recurrence and pharmaceutical analgesia, additional therapy options need to be considered to achieve an optimal symptom control in patients with endometriosis(Horne et al., 2017). In this context, finding ways to prevent or contend with the development of *central sensitization*, and as a result chronic pain, may be a key step toward addressing the issue. The enhanced sensitivity to pain (e.g. toward thermal pain or application of pressure or electrical energy) in women with CPP both with and without endometriosis (Bajaj et al., 2003; Brawn et al., 2014; Laursen et al., 2005) shows that, in both conditions, the experience of pain is deeply altered. Therefore, besides the morphometric and connectivity evaluation based on neuroimaging techniques, stimulation of pain receptors in the peripheral tissues through mechanical (pressure, pinch) pain perception tasks, and pain modulation with emotional stimuli, may afford more insight into the perception of pain in patients with CPP in general and with endometriosis in particular. Although the thermal, pressure or chemical stimuli of pain perception tasks are not directly related to the perception of visceral internal pain, they can point to the dysregulation between the mPFC and the networks involved in different levels of pain processing, possibly revealing the differences between brain alterations related to endometriosis or CPP. A neuroimaging assessment of mPFC activity based on nociceptive stimulation can shed light on how pain information (pain stimuli or nociceptive stimuli) is integrated with memory, mood or spatial awareness (Ong et al., 2019). The development of tasks that can help assess visceral pain sensation more directly ought to be another important goal.

As pain includes a component of unpleasantness, triggering the aversive drive to eliminate the cause, it is often described by adjectives (e.g. nagging, uncomfortable, excruciating) that do not accurately reflect the sensory experience. Changes in mood also influence the affective aspects of pain perception (Institute of Medicine, 1987). Therefore, exploring the interconnection between pain and mental health conditions through multimodal means, including neuroimaging, may help pave the way for effective, individualized treatment of endometriosis. Factors such as distraction, positive mood, and anticipation of (placebo-induced) pain relief have been found to mitigate pain by exerting influence on the mPFC, making it a promising target region for pain therapy (Kummer et al., 2020). Additionally, novel therapies targeting the activity of nerves both in the endometriosis lesions and the nervous system through inhibition of nociceptive ion channels or neuropeptides involved in generating hyperalgesic reactions (e.g. calcitonin gene-related peptide) may add to the multimodal therapy concepts (Saunders & Horne, 2021).

Although the link between mental disorders, pain and endometriosis appears to be robust, it is difficult to determine if endometriosis per se is associated with alterations in brain structure, function or connectivity. The observed alterations in brain structure or resting-state connectivity may be due only to comorbid mood disorders and chronic pain. It is unknown if women with endometriosis have structural and connectivity-related brain alterations that are specific to endometriosis. And if the endometriosis brain does exist, we hypothesize that women with endometriosis may demonstrate alterations in the brain regions associated with different levels of pain experience, e.g. the sensory and emotional aspects. In particular, the regions that are known to play a role in central sensitization, like the brain stem, the thalamus and the cerebral cortex, are also likely to be altered by endometriosis. In addition to pain processing, cognitive, emotional or reward resources and functions, overlapping with changes observed in patients with other chronic pain conditions or mental disorders (particularly depressive or anxiety disorders) (Apkarian et al., 2009; Gray et al., 2020; Kaiser et al., 2015; Tatu et al., 2018), are likely to contribute to the formation of the *endometriosis brain*. Thus, alterations in gray matter volume and resting-state connectivity are likely in the regions (such as the amygdala, the mPFC and the anterior cingulate cortex and possibly also the

hippocampus) potentiated by (chronic) pain signals, with the regions, in turn, modulating the signals' salience leading to pain-related memories and behavioral changes. The severity of perceived pain is also likely to correlate with changes in GMV and resting-state connectivity as seen in other patients with chronic pain (Barroso et al., 2021; Napadow et al. 2010; Wood, 2010). However, it is possible that factors other than pain or mental disorders may also induce brain changes in patients with endometriosis. Because hormone therapy is routinely prescribed to patients with endometriosis (Brown et al., 2018), it may be considered as a potential contributing factor to the *endometriosis brain,* and, given its effectiveness with respect to pain relief, the treatment can have a protective effect in some cases, lowering the number of psychiatric comorbidities. Therefore, studies involving patients with asymptomatic endometriosis as well as those aiming to investigate the influence of hormone therapies on brain and mood changes can shed more light on possible pain-independent brain and mood alterations. Altogether, more research is required before any definitive conclusion can be drawn regarding the *endometriosis brain.*

For effective preventive measures and individualized therapeutic approaches toward maximizing treatment success, clinically informative endometriosis subphenotypes need to be accurately categorized by means of multimodal imaging, socio-economic characteristics, clinical-anamnestic data, confirmed diagnosis of comorbidities (e.g. mental disorders), inflammatory status, immunohistochemical analysis of the tissue, genetic analysis and personality and temperament traits. Multimodal neuroimaging approaches combined with reliable diagnostics of comorbid mental disorders will afford a better understanding of the disease, thereby contributing to the development of optimal therapeutic concepts for different subgroups of patients with endometriosis. Finally, the available therapeutic options seem to allow successful treatment of only a part of the patient population with endometriosis. To improve clinical practice, it will be necessary to determine the factors, such as, possibly, comorbid mental disorders and pain as a psychological symptom, that are negatively associated with therapy response following surgery. The identification (prediction) and characterization of patients who experience no (or only marginal) symptom relief following surgical therapy will help lower the rate of unnecessary (repetitive) surgeries and the associated perioperative morbidity. Therefore, larger longitudinal studies are needed to define and validate optimal therapy concepts for different subgroups of patients with endometriosis with respect to the identified psychiatric comorbidities, anamnestic characteristics, and neuroimaging and biological markers predicting therapy response.

5. Conclusion

Based on these studies' objective assessment of psychopathological comorbidities, using clinical diagnostic criteria, we can safely conclude that there is a high prevalence of mental disorders in patients with endometriosis. We postulate that almost one-third of patients need professional psychiatric or psychotherapeutic help for one or several psychiatric conditions.

At the same time, it is clear that very little is known about the structural and functional brain alterations in patients suffering from endometriosis in terms of chronic pain or mental comorbidities and also in relation to the so-called endometriosis brain. A total of only about 30 patients with endometriosis were investigated in these studies by neuroimaging, which is a very small number given the heterogeneity of the condition. This becomes particularly clear in comparison to the neuroimaging studies related to other conditions. For instance, a recent *meta*-analysis on depression has identified as many as 92 studies on brain morphology with 3,000 MDD patients (Gray et al., 2020; Wise et al., 2017) and up to 25 studies on functional connectivity including 560 MDD patients (Iwabuchi et al., 2015; Kaiser et al., 2015). In view of the high prevalence of endometriosis and its profound long-term impact on the life quality of affected women, the paucity of high-quality multimodal research (including neuroimaging) and longitudinal follow-up in this area is striking. Generally, functional brain imaging studies addressing reproductive cycle-related mood disorders ("women-specific conditions" such as depression during female puberty, premenstrual dysphoric disorder, postpartum depression disorder) are quite scarce (Stickel et al., 2019), which is a clear indication of a gender-bias in research against the female population. There is an urgent need to improve awareness and education and adopt effective measures given the high prevalence of endometriosis and its cumulative effect on women's health and well-being across the lifespan. Biomarkers (e.g. neuroimaging, genetic, inflammatory or immunohistochemical biomarkers) and new therapeutics are needed to target the physiological pathways linked to the development, progression and symptom persistence of the disease. It is only through sufficiently powered, collaborative, multidisciplinary research, enabled by funding bodies through prioritization of endometriosis as a critical public health issue, that real progress can be achieved.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Original Article

Gynaecology

Psychological characteristics and structural brain changes in women with endometriosis and endometriosis-independent chronic pelvic pain

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ABSTRACT

STUDY QUESTION: Are there neurobiological changes induced by endometriosis?

SUMMARY ANSWER: Women with endometriosis demonstrate specific neurobiological changes distinct from those in patients with chronic pelvic pain (CPP) in the absence of endometriosis.

WHAT IS KNOWN ALREADY: Endometriosis is a chronic disease affecting women of reproductive age that presents with pain and infertility often accompanied by comorbid mental disorders. Only one study with a number of limitations has investigated changes in gray matter volumes and functional connectivity in a small group of patients with endometriosis.

STUDY DESIGN, SIZE, DURATION: This prospective study recruited 53 women undergoing a laparoscopy due to suspicion of symptomatic endometriosis and 25 healthy, pain-free women. Clinical and psychological characteristics, thermal pain perception, and voxel- and surface-based morphology were assessed in all study participants. Thereafter, the patients underwent a laparoscopy, where endometriosis was either histologically confirmed and removed, or ruled out. Correspondingly, patients were assigned into the group with endometriosis (n ¼ 27) or with endometriosis-independent CPP (n ¼ 26) and compared to the pain-free controls.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The study groups were generally representative for the population of women with endometriosis. Sociodemographic, medical, clinical, and psychological characteristics were collected using various questionnaires and a structured clinical interview. Thermal pain perception and voxel- and surface-based morphometry were assessed using thermode and MRI, respectively.

MAIN RESULTS AND THE ROLE OF CHANCE: Despite comparable pain intensity and burden of mental disorders, both patient groups demonstrated distinct neurobiological patterns. Women with endometriosis exhibited increased gray matter volume (GMV) in the left cerebellum, lingual gyrus and calcarine gyrus, compared to those with endometriosis-independent CPP. Patients with CPP had decreased GMV in the right cerebellum as compared to controls. Dysmenorrhoea severity correlated positively with GMV in the left inferior parietal lobule, whereas depressive symptoms were associated with decreased GMV in the right superior medial gyrus across patient groups. Dyspareunia correlated negatively with cortical thickness in the left inferior temporal gyrus and left middle temporal gyrus.

LIMITATIONS, REASONS FOR CAUTION: The study groups differed in a few baseline-characteristics, including educational levels, smoking and BMI. While measuring pain perception thresholds, we did not attempt to mimic CPP by placement of the thermode on the abdominal wall.

WIDER IMPLICATIONS OF THE FINDINGS: Changes in gray matter volume associated with endometriosis differ from those observed in women with endometriosis-independent CPP. Our results underline an involvement of the cerebellum in pain perception and the pathogenesis of pain associated with endometriosis.

STUDY FUNDING/COMPETING INTEREST(S): This work was funded by the START Program of the Faculty of Medicine, RWTH Aachen, Germany, and supported by the International Research Training Group (IRTG 2150) of the German Research Foundation (DFG)—269953372/GRK2150, Germany. S.T. was supported by postdoctoral fellowship of the Faculty of Medicine, RWTH Aachen, Germany. There are no conflicts of interest.

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Introduction

Endometriosis is a chronic disease characterized by the development of endometrium-like tissue outside the uterus accompanied by inflammation and affecting □10% of women of reproductive age (Siedentopf and Sillem, 2014). Endometriosis presents with infertility and various pain symptoms, including chronic pelvic pain (CPP), dysmenorrhoea, dyspareunia, dysuria, and dyschezia. For a long time, surgical removal of endometriosis followed by adjuvant hormone therapy was considered to be the main treatment modality (Mettler *et al.*, 2014). Despite the best known therapy, many patients experience symptom persistence and consequently undergo repetitive surgeries, posing a true challenge for care givers (Zondervan *et al.*, 2020). The unsatisfactory outcome of the conventional therapy targeting endometriosis lesions, together with a poor correlation between the extent of the disease and pain severity (Zondervan *et al.*, 2020), suggest complex pain pathogenesis in endometriosis. Besides local nociceptive stimuli originating from endometriosis lesions or postoperative scars being amplified by the inflammatory environment, secondary neuropathic mechanisms, and central pain sensitization are also likely to be involved in the generation of pain (Vitonis *et al.*, 2014). Central modulating mechanisms decreasing the pain threshold and altering pain perception could at least partially account for the refractory pain symptoms in women with endometriosis (Nunes *et al.*, 2015).

Given the problems of CPP, infertility and poor quality of life, endometriosis affects not only physical but also sexual, social, and mental well-being of the women concerned (Zondervan *et al.*, 2020), often resulting in comorbid mental disorders, like depressive or anxiety disorders, with varying degrees of severity (Maulitz *et al.*, 2022). Vice versa, personality traits and risk factors for mental disorders can also facilitate the development of endometriosis symptoms or aggravate the course of the disease, for instance via enhancement of the nociceptive neuronal pathways and central pain sensitization. Additionally, risk factors for mental disorders, like stressful life events, induce changes in the hypothalamic–pituitary–adrenal axis and cortisol levels, altering inflammation responses and facilitating the development of endometriosis lesions (Heim *et al.*, 2000; Fries *et al.*, 2005). As chronic pain and mental disorders affect brain anatomy and function (As-Sanie *et al.*, 2016; Henn *et al.*, 2023), the influence of endometriosis on brain morphology can be assumed. However, the current knowledge on this subject remains limited and relies on a very few studies with considerable limitations (As-Sanie *et al.*, 2012; As-Sanie *et al.*, 2016; Beissner *et al.*, 2018). In fact, only As-Sanie *et al.* (2012) have studied the influence of endometriosis on gray matter volume (GMV) in 17 symptomatic and 15 asymptomatic patients with endometriosis, as well as in 6 women with CPP of other origins. In this study, endometriosis was defined as a surgically confirmed disease within the previous three years, whereas no histological conformation was required. Yet, up to 50% of the intraoperative diagnoses of endometriosis by surgeon cannot be confirmed by histological examination (Walter *et al.*, 2001). Furthermore, if endometriosis lesions have been removed during surgery, persisting or recurrent CPP could potentially be attributable to other factors, including concomitant medical conditions or psychosomatic disorders (Asmundson and Katz 2009). Altogether, it remains unclear whether the GMV alterations in brain regions involved in pain perception observed by As-Sanie *et al.* (2012) are indeed unique characteristics of the 'endometriosis brain' or whether they can rather be explained by the influence of chronic pain, mental comorbidities (Maulitz *et al.*, 2022) or other factors.

To improve our understanding of interactions between endometriosis, comorbid mental disorders, chronic pain and brain morphology, we explored GMV, cortical thickness and psychological characteristics, as primary outcomes, in women with current symptomatic and histologically confirmed endometriosis or endometriosis-independent CPP as well as pain-free healthy female controls. Hypothesizing that there are differences in brain morphology between women with and without endometriosis, we analysed the neuroimaging data with respect to anamnestic, clinical, and psychological characteristics of the participants as secondary outcomes.

Materials and methods

Study participants

The current study population represents a part of an ongoing multicentre longitudinal study '*Prediction Of Therapy Response in Endometriosis patients*' (POTRE; DRKS00021236). In this study, women undergoing a laparoscopy due to suspicion of symptomatic endometriosis were recruited between March 2020 and September 2022 at the Departments of Gynecology and Obstetrics of RWTH Aachen University and Otto-von-Guericke University Magdeburg, Germany. For the control group, women without current psychiatric disorders, dysmenorrhoea, CPP, or other symptoms or a personal history of endometriosis were recruited via flyers and personal advertisement at our outpatient departments, among the hospital staff and medical students.

Exclusion criteria for the study participation were age below 18 years, menopause, surgeries for endometriosis within last 5 years, history of a psychotic or manic episode, dependency on psychotropic substances, alcohol or painkiller abuse, current pregnancy, BMI over 35 (due to the functional magnetic resonance imaging (fMRI) scanner characteristics), and insufficient understanding of German, English, or Russian. The study protocol is presented in a flow chart (Fig. 1). During the screening, 160 patients were considered eligible for the study, of whom 107 failed to undergo the fMRI scan because of organizational restrictions associated with the COVID-19 pandemic or contraindications for fMRI (e.g. ferromagnetic implants, large tattoos or tattoos in the head area, heart diseases, epilepsy or claustrophobia).

The study was approved by the ethical commissions of the Medical Faculty, RWTH Aachen University and Otto-von-Guericke University Magdeburg, Germany based on the Helsinki declaration. All participants provided their informed consent.

Questionnaires

The study participants were asked to answer the *EPHect Questionnaire—Standard* (EPQ-S) (Vitonis *et al.*, 2014) to assess personal and medical data, pain characteristics and sociodemographic data. *Pain Catastrophizing Scale* (Sullivan *et al.*, 1995), *Stressful Life Events Screening Questionnaire* (SLESQ) (Goodman *et al.*, 1998), and *Adult Temperament Questionnaire* by Evans and Rothbart (2007) were used to assess pain catastrophizing, traumatic experiences, and personality assessment, respectively. Data on self-esteem, body esteem, and emotional self-efficacy were collected using *Rosenberg Self-Esteem Scale* (RSES) (Rosenberg, 1965), *Body Esteem Scale* (*BES*) (Mendelson *et al.*, 2001), and *Emotional Self-Efficacy in Regulating Negative Emotions* (ESE-NEG) (Gunzenhauser *et al.*, 2013). The *Beck Depression Inventory* (BDI) (Beck *et al.*, 1961) and *State Trait Anxiety Inventory* (STAI) (Spielberger *et al.*, 1983) were applied to evaluate symptoms of depression and anxiety. Finally, health related quality of life and pain were assessed by *Endometriosis Health Profile Questionnaire* (EHP-30, Jones *et al.*, 2001)

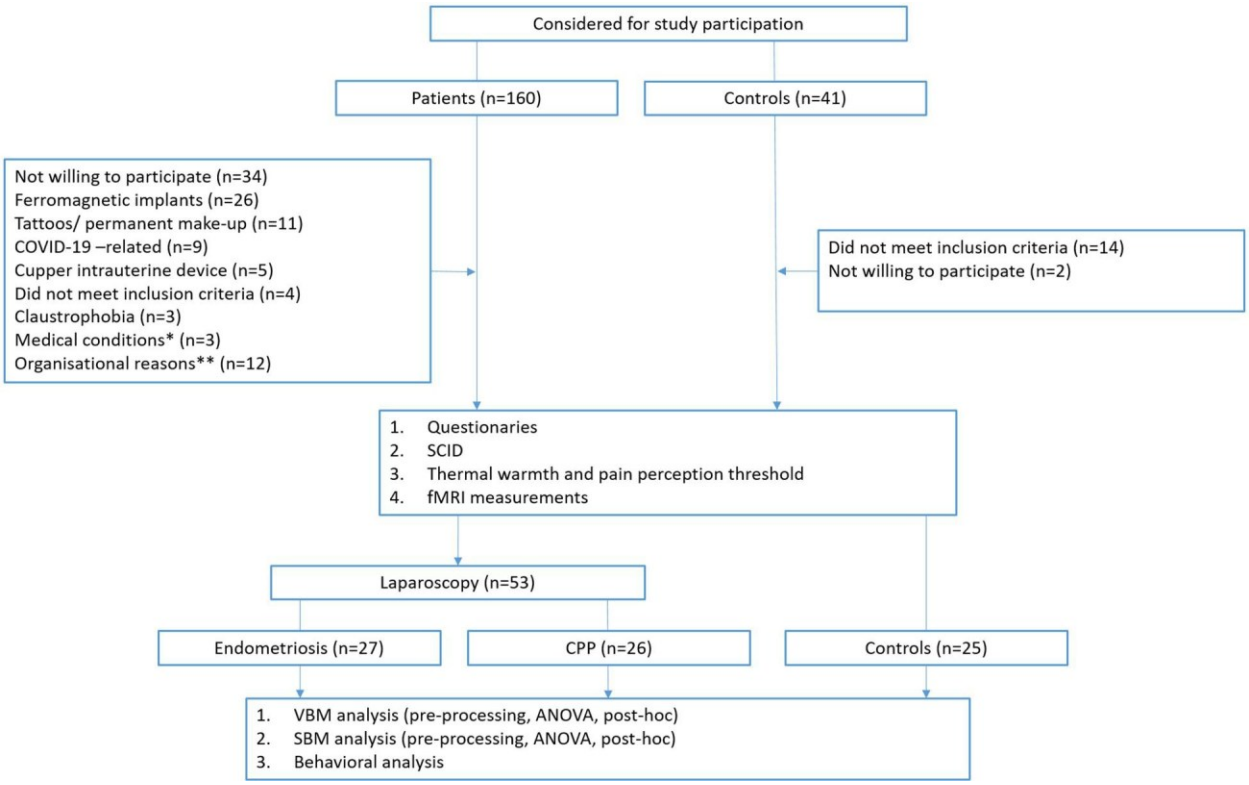

Figure 1. Flow chart of the study design. SCID: Structured Clinical Interview for DSM IV; fMRI: functional magnetic resonance imaging; CPP: chronic pelvic pain; VBM: voxel-based morphometry; ANOVA: analysis of variance; SBM: surface-based morphometry; epilepsy, heart disease; organizational reasons: missing capacity of MRI (n ¼ 5), patient cancelled the planned surgery (n ¼ 3), wrong contact data provided by the patient (n ¼ 3), surgery interruption because of severe intestinal adhesions, no group assignment possible (n ¼ 1).

and *McGill Pain Questionnaire* (SF_MPQ-2) (Melzack, 1987), respectively. Additionally, psychiatric history and potential current disorders were assessed using the *Structured Clinical Interview for DSM IV* (SCID light) (First *et al.*, 2016) by an experienced psychologist.

Pain perception

Thermal warmth and pain perception thresholds were measured by method of limits using a 30 × 30 mm advanced thermal stimulator (thermode, medoc Ltd, Pain & Sensory Evaluation System, PATHWAY) as described by Jo *et al.* (2021).

Neuroimaging

All participants of the study underwent a functional brain MRI examination. For the patients, MRI was performed before planned surgery.

Three Tesla Prisma MR Scanners (Siemens Medical Systems, Erlangen, Germany), located at the Medical Faculties of the RWTH Aachen University and Otto von Guericke University Magdeburg, were utilized to collect the neuroimaging data as described elsewhere (Nehls *et al.* 2024).

The anatomical imaging data were preprocessed using The Computational Anatomy Toolbox (CAT12 Version 12.8) and SPM12 toolbox for Matlab2020b (MathWorks, Inc., Natick, MA, USA) as previously described (Nehls *et al.*, 2024). For normalization, the Geodesic Shooting registration by Ashburner and Friston (2011) was applied. Segmentation of volumes by setting the writing options of the CAT12 toolbox to surface and thickness estimation was utilized to analyse the cortical thickness as previously described (Nehls *et al.* 2024).

Laparoscopy

After enrolment into the study and the above-mentioned examinations, all patients underwent a laparoscopy. During the laparoscopy, the diagnosis of endometriosis was either confirmed and verified by histological examination or ruled out. According to the final diagnosis, the patients were assigned either into the group of endometriosis or CPP. If present, endometriosis lesions were removed and characterized according to the revised American Society for Reproductive Medicine (rASRM) and ENZIAN (Haas *et al.*, 2013).

Statistical analysis

The numerical data were analysed using SPSS® 25 (IBM Corporation, Armonk, NY, USA) for Windows®. One-factorial analysis of variance (ANOVA) for independent samples was applied to analyse continuous measures and the chi square test was used for categorical measures. If the assumption of homogeneity of variance was violated, the independent student t-test for assumed inequality of variance was conducted. *P*-values of <0.05 were chosen to indicate the significance level and the Bonferroni correction was applied for multiple comparisons.

The voxel-based (VBM) and surface-based morphometry (SBM) data were analysed using SPM 12 toolbox for Matlab2021b (MathWorks, Inc., Natick, MA, USA). Smoothed gray matter segments and thickness data were compared by whole-brain one-way ANOVA with the theory of Gaussian random fields between the three study groups by calculation of t-contrasts. To investigate endometriosis-specific GMV changes, we calculated t-contrasts of endometriosis patients against a combined group comprised of CPP patients and healthy controls. The influence of chronic pain on VBM and SBM was evaluated by calculation of

t-contrasts of patients with CPP (with and without endometriosis) against pain-free controls. VBM and SBM analyses were controlled for age and hormonal contraception. As VBM can be influenced by the individual head size, the latter was also corrected for total intracranial volume (TIV) (Barnes *et al.*, 2010).

To explore correlations of dysmenorrhoea and dyspareunia severity with visual analogue scale (VAS), depression scores, pain perception thresholds and GMV and SBM, whole-brain multiple regression analyses were conducted on the entire study population. Since dysmenorrhoea was an exclusion criterion for the control group, the controls were not included into the analysis of correlations between pain, GMV and SBM, respectively. To control for the concurrent influence of pain and depression on VBM, correlations with pain symptoms were controlled for the BDI scores and vice versa. Structures and surfaces were labelled according to the JuBrain Anatomy toolbox for SPM (Eickhoff *et al.*, 2007) and Desikan *et al.* (2006), respectively.

The statistical significance threshold was set at $P < 0.05$ cluster-level Family-Wise Error (FWE)-correction, with a cluster-forming threshold at the voxel-level $P < 0.001$ for VBM and SBM unless otherwise specified. All results are presented in the MNI space.

Results

Population baseline characteristics

The study groups consisted of 27 patients with confirmed endometriosis, 26 patients with endometriosis-independent CPP and 25 healthy female controls, and did not differ significantly with respect to age, menarche, ethnicity, fertility and comorbidities (Table 1). Except one woman with ulcerative colitis (without pain symptoms) in the control group, no study participants suffered from inflammatory bowel diseases or interstitial cystitis. In the endometriosis group, 13, 7, 3, and 4 patients had stage I, II, III, and IV disease according to the rASRM classification, respectively. There were 16 patients with deep infiltrating endometriosis lesions: 5 had ENZIAN A1-2, 15 had ENZIAN B1-3, 3 had ENZIAN C1-2, and 5 had ENZIAN FI, FB, FU, or FO (diaphragm). The healthy controls had lower BMIs, no previous laparoscopies and were less likely to use pain killers within the last three months as compared to both patient groups ($P < 0.05$; $P < 0.01$, and $P < 0.01$, respectively). Patients with endometriosis more often reported a family history of CPP and smoked more frequently ($P < 0.05$) as compared to the other two study groups. Interestingly, more women with endometriosis-independent CPP used hormonal contraception within the last three months as compared to those with endometriosis ($P < 0.05$). Women with CPP with and without endometriosis had similar pain severity as evaluated by the VAS. According to the SCID light, the prevalence of mental disorders was the highest among women with endometriosis-independent CPP; however, the differences between both patient groups did not reach the level of significance.

Behavioural data and pain perception

No differences were observed between the study groups in terms of self-esteem, stressful live events, regulating distress or anger, perception of own appearance and weight, negative affect, extraversion or orienting sensitivity, thermal warmth, and pain perception (Table 2). Independent of endometriosis, women with CPP scored significantly higher in rumination, helplessness, and reinforcement ($P < 0.01$) on the *Pain Catastrophizing Scale* as compared to the controls. Altogether, 15% of women with endometriosis, 23% with CPP and no controls reached the clinically relevant level of pain catastrophizing (>30).

Compared to the controls, endometriosis patients were less able to express positive emotions ($P < 0.01$), whereas women with endometriosis-independent CPP showed lower effortful control in the *Adult Temperament Questionnaire* ($P < 0.01$) and greater state and trait anxiety in *the STAI* ($P < 0.05$; $P < 0.01$, respectively). Regardless of endometriosis, women with CPP had higher *BDI* scores ($P < 0.001$) and poorer outcomes for pain, powerlessness, emotional well-being, social support, and self-image in the *EHP-30* ($P < 0.001$) as compared to the controls. Moreover, *BDI* scores and severity of dysmenorrhoea correlated significantly ($P < 0.001$).

Patients with CPP demonstrated less positive attribution as compared to patients with endometriosis based on the *BES* ($P < 0.05$).

VBM analyses

As compared to patients with CPP, women with endometriosis showed greater GMV in the left cerebellum and lingual gyrus (FWE cluster correction level with a cluster-forming threshold at $P < 0.001$; $P < 0.05$; $k = 773$) and in the left calcarine gyrus (uncorrected threshold at $P < 0.001$; $P < 0.05$; $k = 408$) (Fig. 2). Patients with endometriosis-independent CPP had smaller GMV in the right cerebellum (right lobule VIIa crusI (hem)) than the healthy controls (uncorrected threshold at $P < 0.001$; $P < 0.05$; $k = 400$, Fig. 3).

As compared to all participants of the study without endometriosis, patients with endometriosis had increased GMV in the right cerebellum and fusiform gyrus (uncorrected threshold at $P < 0.001$; $P < 0.05$; $k = 645$) and in two clusters in the left cerebellum, one of them extending to the left fusiform gyrus (FWE cluster correction level with a cluster-forming threshold at $P < 0.001$; $P < 0.05$; $k = 1101$ and with uncorrected threshold at $P < 0.001$; $P < 0.05$; $k = 618$, respectively). After controlling for chronic pain, the differences remained significant only in the both left cerebellum clusters. Furthermore, a GMV increase in a third cluster involving the left calcarine gyrus became significant with uncorrected threshold at $P < 0.001$ ($P < 0.05$; $k = 571$). No differences were found between the pain-free controls and women with CPP (with and without endometriosis).

To exclude influence of smoking on our results, we performed additional analyses with a correction for smoking. In these analyses, the above-mentioned VBM differences between the groups hardly changed; only endometriosis patients showed two additional clusters with greater GMV as compared to the CPP group: the right inferior parietal lobule, extending to the right angular gyrus and the right precentral gyrus/right inferior frontal gyrus (uncorrected threshold at $P < 0.001$; $P < 0.005$; $k = 460$ and $k = 377$, respectively).

Multiple regression analyses

Dysmenorrhoea severity correlated positively with GMV in the left inferior parietal lobule (IPL), even after controlling for the *BDI* scores (uncorrected threshold at $P < 0.001$; $P < 0.05$; $k = 444$; $P < 0.05$; $k = 464$, respectively, Fig. 4). No statistically significant correlation could be observed between the severity of dyspareunia and GMV.

Clinically relevant depression (*BDI* scores ≥ 14) was associated with decreased GMV in the right middle fontal gyrus (MFG) and absolute values for the *BDI* scores with increased GMV in the right superior medial gyrus (SMG) (uncorrected threshold at $P < 0.001$; $P < 0.05$; $k = 631$ and $P < 0.05$; $k = 473$, respectively, Fig. 4). However, the correlations disappeared after controlling for the dysmenorrhoea severity.

Table 1. Population baseline characteristics.

	Endometriosis n ¼ 27	CPP n ¼ 26	Controls n ¼ 25	*P*-value
Age	27 (19–50)	24.5 (18–44)	26 (18–39)	0.439
Ethnicity				
European	92	88	87	0.972
Asian	4	4	9	
Other	4	8	4	
Educational status				
Secondary school	65	52	25	0.023§
University	28	36	75	
Post-secondary non-tertiary education	7	12	0	
Smoking	33	8	5	0.021§
BMI	23 (17–38)	22 (18–43)	20 (18–25)	0.011#
Menarche age	13 (9–17)	13 (10–16)	13 (10–15)	0.557
VAS dysmenorrhoea for the past 12 months	9 (0–10)	8 (0–10)	0	0.103
VAS dyspareunia	1 (0–10)	0 (0–10)	0	0.754
Hormonal treatment/contraception				
Within past 3 months	24	64	56	0.016□
History	84	72	65	0.344
Previous pregnancies	15	19	8	0.602
Infertility	31	11	6	0.087
Other pain conditions	58	60	37	0.249
Previous laparoscopies	33	32	0	0.004§#
Personal history of endometriosis§§	48	23	0	0.14
Based on laparoscopy	30	16	0	
Family history□□ of endometriosis	31	16	6	0.121
Family history□□ of CPP	42	40	6	0.024§
History of pain killers intake□□□	77	75	32	0.003§#
SCID				
Previous psychiatric disorder	67	80	21	<0.001§#
Depressive disorder	52	31	16	0.028§
Post-traumatic stress disorder	26	42	8	0.010#
Panic disorder	19	19	0	0.052
Generalized anxiety disorder	4	0	0	1.000
Current psychiatric disorder	44	56	0	<0.001§#
Depressive disorder	15	23	0	0. 036#
Post-traumatic stress disorder	11	0	0	0.103
Panic disorder	11	15	0	0.158
Generalized anxiety disorder	22	19	0	0.41§

Age, BMI, menarche and visual analog scale (VAS) scores are presented in median with range in parenthesis and the remaining data are presented in %.
Statistically significant differences detected between the following groups:.
□ Patients with endometriosis vs. women with endometriosis-independent chronic pelvic pain (CPP).
§ Patients with endometriosis vs. controls.
# Patients with CPP vs. controls.
§§ Question on personal history of endometriosis could be answered positively, if endometriosis was diagnosed in a surgery, with MRI or sonography or based on symptoms.
□□ Family history refers to relatives of first (mother, sister) and second (aunt, grandmother, cousin) grade.
□□□ History of pain killer intake is defined as therapy at least once a week over at least 3 months. Structured Clinical Interview for DSM IV: (SCID).

Thermal pain perception thresholds correlated negatively with GMV in the right fusiform gyrus, right thalamus, extending to hippocampus, and parahippocampal gyrus (uncorrected threshold at $P < 0.001$; $P < 0.05$; $k ¼ 708$, Fig. 4).

Controlling for smoking hardly changed the results of multiple regression analyses except an additional cluster in the right precuneus, where GMV negatively correlated with clinically relevant depression (uncorrected threshold at $P < 0.001$; $P < 0.05$; $k ¼ 641$) and the correlation between thermal pain thresholds and GMV focused in the right fusiform gyrus (uncorrected threshold at $P < 0.001$; $P < 0.05$; $k ¼ 402$).

SBM analyses

No differences in the cortical thickness independent of smoking could be detected between the study groups. The severity of dyspareunia correlated negatively with the cortical thickness in the left inferior temporal gyrus and middle temporal gyrus (FWE cluster correction with voxel-forming threshold at $P < 0.001$), even after controlling for the *BDI* scores ($P < 0.05$; $k ¼ 150$ and $k ¼ 154$, respectively; Fig. 5). No correlations could be found between cortical thickness and severity of depressive symptoms, clinically relevant depression, or dysmenorrhoea.

Discussion

In the present study, we investigated psychological characteristics, thermal pain perception and brain morphology of women with symptomatic endometriosis, CPP and healthy controls. Our study population comprised of premenopausal women and the groups were comparable with respect to age, menarche, and ethnicity, but differed in a few socioeconomic and medical-anamnestic parameters. Both patient groups reported on severe disabling dysmenorrhoea. More than half of the patients suffered from other comorbid pain disorders and one third of them already had undergone at least one laparoscopy. Compared to the controls, both patient groups reported more frequently on family history of CPP and endometriosis, suggesting familial clustering and supporting genetic predisposition to these conditions (Zondervan *et al.*, 2020).

Table 2. Results of the questionnaires and thermal perception assessment.

	Endometriosis n ¼ 27	CPP n ¼ 26	Controls n ¼ 25	*P*-value
Pain Catastrophizing Scale				
Helplessness	11 (0–21)	12 (2–25)	0 (0–10)	<0.001§#
Reinforcement	4 (0–6)	3 (0–16)	1 (0–7)	0.006§#
Rumination	8 (2–15)	8 (0–12)	4 (0–12)	0.005§#
Regulation of emotions				
Expressing positive emotions	16 (9–20)	16 (11–74)	18 (15–20)	0.004§
Regulation distress	8 (5–12)	9 (3–42)	10 (4–12)	0.558
Regulation anger	9 (3–15)	10 (3–33)	10 (6–12)	0.738
Body perception				
Appearance	38 (23–47)	36 (16–48)	39 (27–47)	0.180
Weight	20 (8–28)	19 (6–30)	21 (12–29)	0.234
Attribution	16 (11–23)	13 (5–19)	17 (9–20)	0.019
Temperament				
Negative affect	97 (60–130)	103 (11–150)	89 (47–110)	0.115
Effortful control	82 (51–103)	73 (39–106)	87 (63–105)	0.005#
Extraversion	94 (61–113)	92 (56–122)	92 (71–110)	0.778
Orienting sensitivity	74 (24–91)	68 (28–100)	64 (36–86)	0.238
Stressful live events	70%	76%	53%	0.228
BDI	14 (0–30)	11 (0–63)	2 (0–14)	<0.001§#
STAI State	46 (20–62)	49 (36–62)	43 (26–48)	0.039#
STAI Trait	49 (24–61)	50 (40–69)	44 (32–51)	0.009#
Self-esteem	18 (10–30)	19 (10–36)	15 (10–29)	0.244
EHP-30				
Pain	56 (24–98)	60 (20–91)	20 (20–35)	<0.001#§
Control/powerlessness	49 (23–77)	54 (20–80)	17 (17–34)	<0.001#§
Emotional well-being	53 (17–74)	46 (17–80)	17 (17–49)	<0.001#§
Social support	65 (20–95)	50 (5–100)	20 (20–40)	<0.001#§
Self-image	40 (20–93)	37 (20–100)	20 (20–40)	<0.001#§
Thermal warmth perception threshold	39 (35–46)	39 (36–48)	39 (36–49)	0.655
Thermal pain perception threshold	46 (43–50)	46 (39–50)	46 (42–50)	0.931

The data are presented as median with range in parenthesis, except for the stressful live events, which are presented as a frequency of at least one event within the group. Thermal warmth and pain perception thresholds are expressed in Celsius. Statistically significant differences detected between the following groups:
 patients with endometriosis vs. women with chronic pelvic pain (CPP);
§ patients with endometriosis vs. controls;
# patients with CPP vs. controls.
BDI: Beck Depression Inventory; STAI: State Trait Anxiety Inventory; EHP-30: Endometriosis Health Profile Questionnaire.

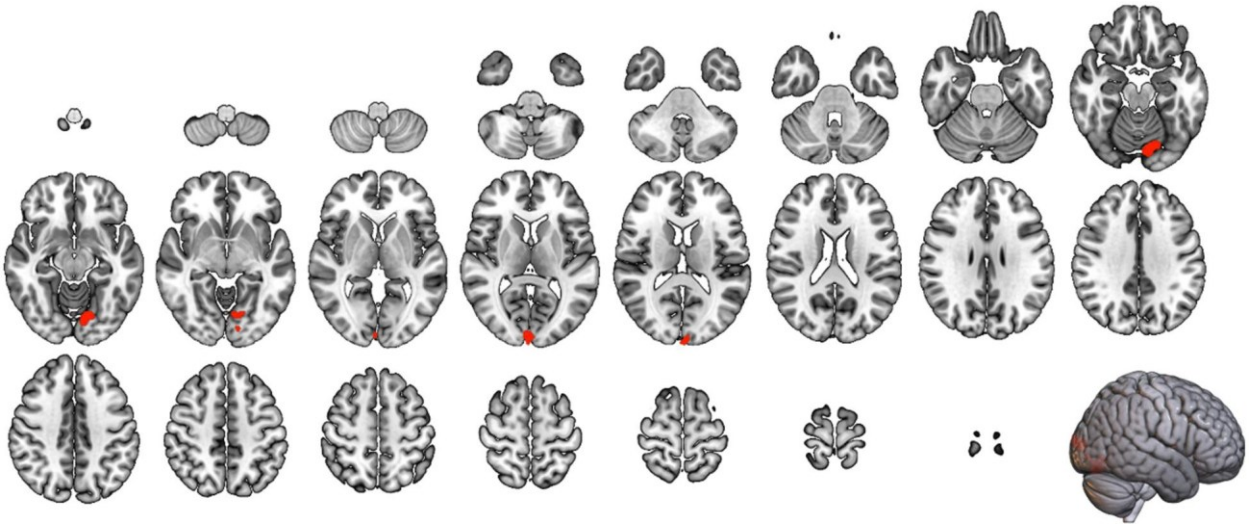

Figure 2. Increased gray matter volume in women with endometriosis as compared to CPP patients. Axial view with slices z-coordinates at −64, −58, −52, −44, −38, −32, −26, −18, −12, −6, 2, 8, 14, 20, 28, 34, 40, 48, 54, 60, 66, 74, 80, respectively and sagittal view from right. Cross-sectional whole brain ANOVA revealed increased gray matter volume (GMV) in the left cerebellum and the left lingual gyrus (FWE corrected $P < 0.05$; k ¼ 773) and in the left calcarine gyrus (uncorrected threshold at $P < 0.001$; $P < 0.05$; k ¼ 400) in women with endometriosis (n ¼ 27) as compared to patients with endometriosis-independent chronic pelvic pain (CPP) (n ¼ 26). Visualized with MRIcroGL (Rorden, 2022).

Even though hormonal treatment is recognized as first-line therapy of endometriosis (Mettler *et al.*, 2014), fewer women with endometriosis were taking hormonal therapy within 3 months before the study enrolment as compared to other study groups. A possible explanation for this could be a selection bias due to more frequent admission to surgery of women with endometriosis

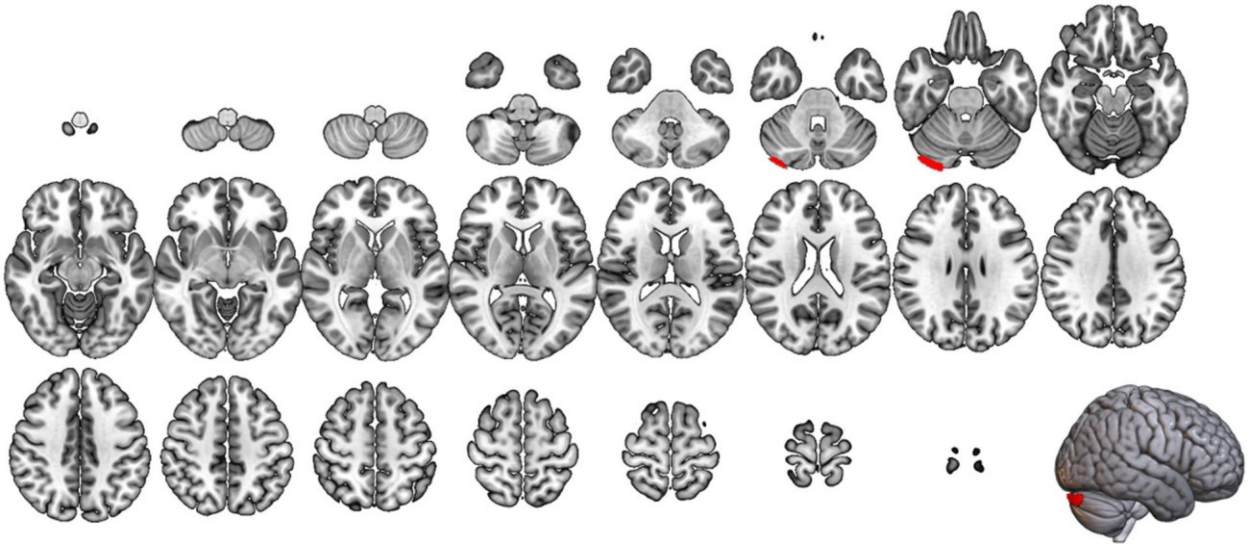

Figure 3. Decreased gray matter volume in women with endometriosis-independent CPP as compared to the control group. Axial view with slices z-coordinates at −64, −58, −52, −44, −38, −32, −26, −18, −12, −6, 2, 8, 14, 20, 28, 34, 40, 48, 54, 60, 66, 74, 80, respectively and sagittal view from right. Cross-sectional whole brain ANOVA revealed decreased gray matter volume (GMV) in the right cerebellum (k ¼ 408; uncorrected threshold at $P < 0.001$; $P < 0.05$) in patients with endometriosis-independent chronic pelvic pain (CPP) (n ¼ 26) as compared to the controls (n ¼ 25). Visualized with MRIcroGL (Rorden, 2022).

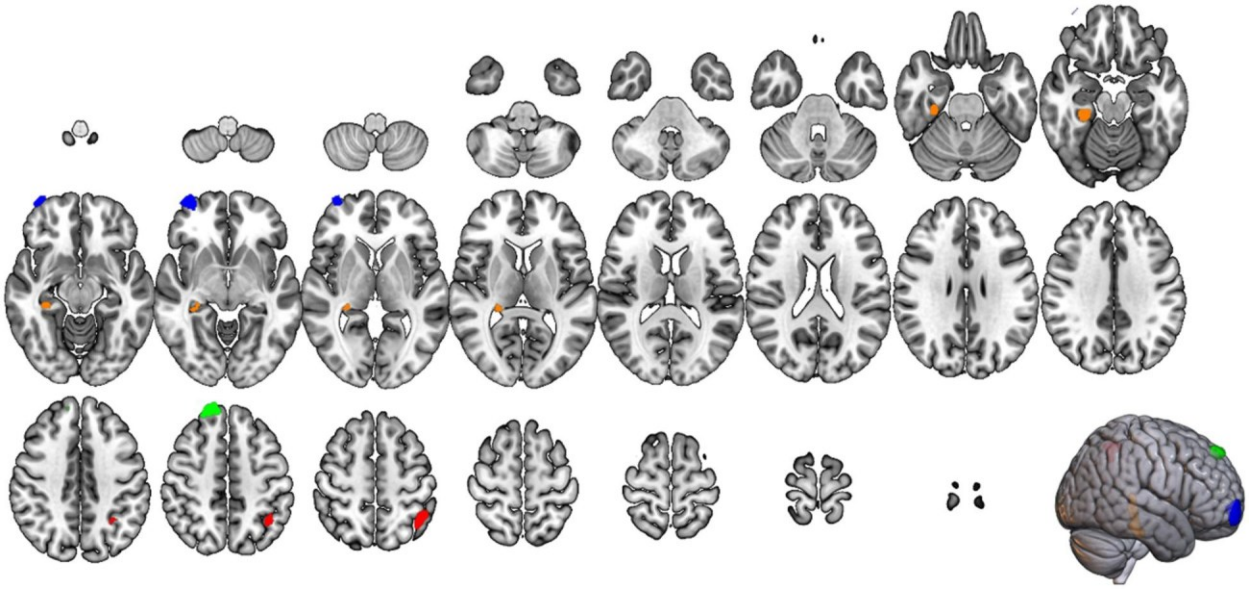

Figure 4. Correlations between pain, depression scores and gray matter volume. Axial view with slices z-coordinates at −64, −58, −52, −44, −38, −32, −26, −18, −12, −6, 2, 8, 14, 20, 28, 34, 40, 48, 54, 60, 66, 74, 80, respectively and sagittal view from right. Whole-brain multiple regression analysis showed a positive correlation between the severity of depressive symptoms (BDI scores) and gray matter volume (GMV) in the right superior medial gyrus (uncorrected threshold at $P < 0.001$; $P < 0.05$; k ¼ 473; green) and a negative correlation between the clinically relevant depression (BDI score of 14 and higher) with GMV in the right middle frontal gyrus (uncorrected threshold at $P < 0.001$; $P < 0.05$; k ¼ 631; blue). The dysmenorrhoea severity on visual analog scale was associated with an increase of GMV in the left inferior parietal lobule (uncorrected threshold at $P < 0.001$; $P < 0.05$; k ¼ 444; red). A negative correlation was found between the thermal pain perception threshold and GMV in the right fusiform gyrus and right thalamus (uncorrected threshold at $P < 0.001$; $P < 0.05$; k ¼ 708; orange). All study participants were included in the analyses (n ¼ 78) except for the analysis of the impact of dysmenorrhoea on VBM, where only the patient groups were included (n ¼ 53). Visualized with MRIcroGL (Rorden, 2022).

because of infertility, while trying to conceive. In line with this, women with endometriosis suffered from infertility almost three times more often than patients with CPP and the rate of previous hormone intake did not differ between the groups. Another surprising finding of our study was the higher frequency of smoking among endometriosis patients. The data on smoking and endometriosis remain controversial, however in our study, smoking women with CPP had about six times higher probability of being diagnosed with endometriosis as compared to those who did not smoke.

Comorbid mental symptoms and behavioural parameters

In alignment with previous studies (Siedentopf and Sillem, 2014; Maulitz *et al.*, 2022), we found a much higher burden of psychiatric comorbidities in our patient groups as compared to the

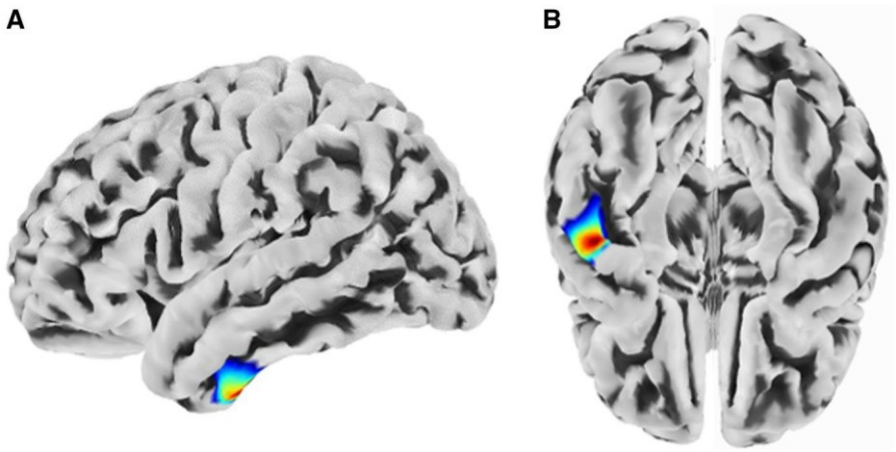

Figure 5. Correlation between cortical thickness and dyspareunia severity. (**A**) Sagittal view from left. (**B**) Axial view from below visualized with CAT12 Version 12.8. The coloured areas show the negative correlation between the dyspareunia severity and cortical thickness in the left inferior temporal gyrus and the left middle temporal gyrus ($P < 0.05$; k ¼ 154) in patients with chronic pelvic pain (CPP) with and without endometriosis (n ¼ 53). Visualized with CAT12 Version 12.8.

prevalence in the global female population with 4.54% and 5% for depression and anxiety, respectively (Institute for Health Metrics and Evaluation (IHME), 2020). Rates of self-reported psychological symptoms are proven to be higher than those if diagnostic tools, like interview were applied (Levis *et al.*, 2019) and reach 86% for depression in endometriosis patients (Lorencatto *et al.*, 2006). Based on the *SCID*, we found somewhat lower frequencies of mental disorders in our study groups. As a predominant proportion of patients with depression report some sort of chronic pain (Bair *et al.*, 2003), depression is likely to be overpresented among patients with CPP of unknown origin, explaining the high rate of mental disorders in our group with endometriosis-independent CPP. In the study of As-sanie *et al.* (2012, 2016), patients with CPP regardless of endometriosis, suffered more often from depressive mood than asymptomatic women, suggesting a major role of pain in the development of depression. The relationships between pain and mental disorders are likely to have a complex reciprocal pattern, labelled as depression-pain dyad (Bair *et al.*, 2003), with both possibly mutually exacerbating and chronifing each other. Physiologically, the pain modulation system can amplify or dampen pain impulses and determine vigilance to external threats or sensations originating inside the body. Dysfunction of this system, for instance due to mental disorders, can lead to amplification of even minor pain stimuli focusing patient's attention on the symptoms. Patients with abdominal pain are especially predisposed to depression and anxiety (Walter *et al.*, 2013). In turn, mental disorders and catastrophizing also adversely affect the course of pain conditions (Asmundson and Katz, 2009). Given similar (high) pain intensity in both our patient groups, it was not surprising that they demonstrated comparable catastrophizing scores. Treatment of single aspects of the depression-pain dyad or anxiety has proved to be rather unsuccessful (Bair *et al.*, 2003; Beissner *et al.*, 2018) and our data support necessity of multimodal therapy of endometriosis. Interestingly, anxiety could be reduced upon psychotherapy combined with somatic stimulation in symptomatic patients with endometriosis (Beissner *et al.* 2018).

Moreover, post-traumatic stress disorder was also frequent among our patients. Early stressful live events can facilitate an inadequate regulation and expression of emotions leading to ruminative responses to distress but can also contribute to the pathogenesis of symptomatic endometriosis (Harris *et al.*, 2018). We observed impaired expression of positive emotions in endometriosis patients and lower social self-esteem in women with endometriosis-independent CPP. Independent of endometriosis, patients demonstrated worse social support and self-image as compared to the healthy controls, most likely reflecting the influence of chronic pain rather than endometriosis itself.

Gray matter volume differences between the study groups

The main finding of our study was that patients with CPP in the presence and absence of endometriosis develop particular GMV patterns. Women with endometriosis had increased GMV in the left cerebellum, lingual gyrus and calcarine gyrus as compared to patients with CPP, whereas patients with endometriosis-independent CPP demonstrated decreased GMV in the right cerebellum as compared to the controls. Declines in the GMV is most likely to be explained by neuronal loss or changes in synaptic density due to excessive noxious stimulation in the corresponding brain regions, whereas increased GMV can reflect a local adaptation to elevated neural activity (Liu *et al.*, 2023). Traditionally, the cerebellum has been considered as brain region responsible for motor control. Only recently, the involvement of the cerebellum in nociception and emotion regulation has became of interest (Moulton *et al.*, 2010).

Numerous studies have demonstrated activation of the cerebellum upon pain stimuli, but its exact role in pain perception has not been sufficiently elucidated up to date. *In vivo*, the cerebellum was shown to participate in the processing of afferent signals from cutaneous and visceral nociceptors, yet its involvement in the circuits of visceral pain seems to be greater than in somatic pain (Claassen *et al.*, 2020). The putative functions of the cerebellum in pain processing are apparently not limited to nociceptive-specific activation but also encompass other processes related to pain experience, like anticipation of pain, withdrawal responses (Moulton *et al.*, 2010) and temporal expectations (Breska and Ivry, 2021). Given the cyclic nature of menstruation and conscious initiation of sexual intercourse, expectancy, rhythm- and interval-based modulation of the pain circuits can be particularly expressed in women suffering from dysmenorrhoea and dyspareunia and may account for the observed changes in the cerebellum.

Despite similar intensity of pain symptoms, both patient groups demonstrated distinct cerebellar alterations. CPP was associated with a GMV decrease in the right cerebellum possibly

attributed to pain, mental disorders or a combination of both. In contrast, women with endometriosis demonstrated a GMV increase in cerebellum that could counterbalance pain-induced alterations and explain why no GMV difference in the right cerebellum was found between women with endometriosis and controls. This hypothesis was further supported by the fact that the GMV increase in the right cerebellum in the endometriosis group as compared to the women without endometriosis disappeared after controlling for pain in the analysis. An alternative explanation for the VBM differences between the patient groups could be a variability of the neural footprint dependent on whether it was created by depression with secondary pain symptoms or by a pain condition with secondary comorbid depression. As one may hypothesize that the proportion with primary depression with concomitant pain was higher in the CPP group and that secondary depressive disorder was more prevalent among endometriosis patients, different brain regions may be involved despite similar clinical outcomes (Zheng *et al.*, 2022).

Compared to patients with CPP, women with endometriosis demonstrated increased GMV in the left calcarine and lingual gyrus—regions primarily associated with the visual cortex but also related to fear processing (Zhang *et al.*, 2016), emotional pain modulation (Mayr *et al.*, 2022), and mental disorders (Luo *et al.*, 2022). These processes may contribute to the neurobiological changes associated with endometriosis, even though we could not detect differences in clinical and behavioural parameters between our patient groups, possibly due to the relatively small sample size. Alternatively, these changes might result from central compensatory mechanisms facilitating coping with endometriosis symptoms. Inclusion of smoking as a covariate into the analysis additionally revealed greater GMV in the regions associated with nicotine dependency (Brown *et al.*, 2023; Claus *et al.*, 2013) and cue-reactivity towards cues of an addiction (Zeng *et al.*, 2021) in women with endometriosis as compared to the CPP patients, and their involvement (Courtney *et al.*, 2014) in the observed correlation with clinically relevant depression in our population.

The only published work on the influence of endometriosis on brain morphometry found a GMV decrease in the left thalamus, cingulate gyrus, right putamen and insula in women with symptomatic endometriosis (As-Sanie *et al.*, 2012). Different definitions of endometriosis, missing data correction for TIV or hormonal contraception preclude a valid comparison of this study with our results. For instance, dysmenorrhoea was defined as pelvic pain on 5 or more days of each menstruation. However, already 1–3 days of menstrual pain can influence GMV (Tu *et al.*, 2013). Recently, Liu *et al.* (2023) demonstrated GMV decrease in brain regions involved in emotional and sensory aspects of pain in women with primary dysmenorrhoea. However, no alterations in the cerebellum were detected in this study, possibly due to an only marginal overlap of this population with our CPP group. Additionally, MRI was performed during menstruation, therefore the observed neuroanatomical changes can encompass a combination of chronic alterations with acute, functional responses to the painful stimuli differing from measurements outside menstruation.

Association of gray matter volume with clinical and psychological characteristics

In our study, severity of depression correlated with GMV in the right SMG that is part of the supplementary motor area (Wei *et al.*, 2021). As this correlation disappeared after controlling for dysmenorrhoea in the analysis, and taking into account correlation of *BDI* scores with dysmenorrhoea, these alterations can rather be attributed to chronic pain reflecting interactions within the pain-depression dyad. Further, *BDI* scores were associated with reduced GMV in the right MFG, a region participating in generation and regulation of negative emotions and involved in social anxiety disorder (Liang *et al.*, 2023). Interestingly, the right MFG is also responsible for the modulation of endogenous and exogenous awareness, interrupting endogenous attributional processes and reorienting the attention to exogenous stimuli (Japee *et al.*, 2015). Malfunction of these processes may play a role in excessive focusing on visceral nociceptive stimuli with pain-related anxiety and engagement in hypervigilance deteriorating CPP.

Dysmenorrhoea severity was associated with structural changes in the left IPL. Among other functions, this region participates in formation of pain-associated memory and becomes activated during remembrance of prior painful experiences, possibly explaining its involvement in such periodically repeating events as dysmenorrhoea (Upadhyay *et al.*, 2016).

Thermal pain perception

We could not confirm the higher pain sensitivity in women with CPP observed in other studies (Grundstro€m *et al.*, 2019). This could be explained by differences in the thermode placement, since we did not try to mimic the localization of dysmenorrhoea symptoms by placing the thermode on the abdominal wall. Nevertheless, in line with other observations (Damascelli *et al.*, 2022), the pain perception thresholds correlated negatively with GMV in the right fusiform gyrus and right thalamus, extending to the right hippocampus and parahippocampal gyrus, regions involved in the sensorimotor network of the pain matrix, default mode network (DMN). In contrast, As-sanie *et al.* (2012) found an association between pressure pain perception threshold on the thumb and GMV in the mid-cingulate cortex. The variation of these findings underlines multifaceted nature of pain perception.

Surface-based morphometry

Our study was the first to investigate cortical thickness in patients with endometriosis. No differences could be found between the study groups. However, pain symptoms were associated with reduced cortical thickness in the left inferior and middle temporal gyrus. Both these regions are related to the DMN that is likely to link environmental stimuli, including pain with personal experience and memory and is involved into the pathogenesis of pain disorders such as fibromyalgia and lower back pain (Fallon *et al.*, 2016; Alshelh *et al.*, 2018). The inferior and middle temporal gyri are thought to regulate pain-related attention and emotions, possibly increasing the focus on pain-related experiences and rumination (Li *et al.*, 2020). Dampened deactivation in these regions may contribute to a prolongation of pain sensation (Mayr *et al.*, 2022). The observed morphometric changes may reflect neurobiological processes involved in enhanced focusing on painful intercourse, catastrophizing and pain avoiding behaviour.

Limitations and strengths

In this prospective study, we investigated GMV and cortical thickness in patients with symptomatic endometriosis and endometriosis-independent CPP with respect to psychological covariates. A few limitations have to be considered. First of all, the relatively small sample size and a few differences in the baseline characteristics may affect the robustness and generalizability of the results. Compared to the patients, the controls had higher educational levels, probably due to the recruitment at the university hospital, attracting staff and leading to an over-presentation

of academics. The CPP group possibly includes women with various somatic and psychosomatic pain causes, though all patients were examined by an experienced gynaecologist before surgery and a large number of clinically relevant differential diagnoses were excluded. Additionally, all groups might have included patients with adenomyosis uteri and the measurements were performed independently of menstrual cycle.

A few women with previous surgery for endometriosis were included into the CPP group, and therefore, permanent endometriosis-induced changes in VBM could not be excluded. However, considerable neuroplasticity depending on the pain character, therapy and psychologic state was demonstrated before for various patient collectives (Naegel *et al.*, 2014; Beissner *et al.*, 2018). Moreover, as GMV is likely to change in opposite directions in both study groups, the influence of previous endometriosis would only reduce differences between the groups. Asymptomatic endometriosis cannot be completely excluded in the healthy controls. Taking into account the prevalence of asymptomatic endometriosis in general population of □4.4% (Parazzini *et al.*, 2020), we might have included one woman with asymptomatic endometriosis in our control group, which would not considerably influence the results. Hormones might also influence brain structures (Toffoletto *et al.*, 2014), but all neuroimaging analyses were controlled for hormonal therapy.

The strength of our study was the prospective design, where women with severe CPP and an indication to laparoscopy underwent the study examinations before ruling out or confirming endometriosis. All endometriosis cases were histologically confirmed, and the operationalization of the endometriosis group did not relay on merely anamnestic history and the knowledge on the presence of the disease could not influence the results. The confounders were limited and the groups were balanced with respect to age. Additionally, we gained information on great number of clinical, behavioural, and psychological parameters that could be related to the neuroimaging data.

In conclusion, women with CPP with and without endometriosis, demonstrated a high burden of psychological distress. Depressive symptoms were associated with alterations in the brain regions involved into the modulation of endogenous and exogenous awareness, possibly facilitating a re-orientation of the personal focus towards endogenous (painful) stimuli. Severity of dysmenorrhoea correlated with changes in the brain areas participating in formation of pain-associated memory. Our data suggest an important role of the cerebellum in pain regulation and its involvement in alterations associated with endometriosis. Further evidence is required to elucidate the role of the cerebellum in endometriosis and shed light on the interrelations between disease symptoms and neurobiological changes.

Data availability

Data cannot be shared for ethical/privacy reasons.

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Authors' roles

L.M.: recruitment, data collection, analyses, writing of original draft; S.N.: methodology, reviewing; E.S.: resources, reviewing; A. I.: resources, reviewing; T.K.: clinical support, reviewing; A.T.H.: analysis, reviewing; N.C.: conceptualization, methodology, resources, reviewing; S.N.T.: conceptualization, methodology, project administration and supervision, manuscript correction.

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Conflict of interest

None declared.

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Erklärung § 5 Abs. 1 zur Datenaufbewahrung

Hiermit erkläre ich, dass die dieser Dissertation zu Grunde liegenden Originaldaten

- in der Klinik für Gynäkologie und Geburtsmedizin des Universitätsklinikums Aachen

hinterlegt sind.

Erklärung gemäß § 5 Abs. (1) und (2), und § 11 Abs. (3) 12. der Promotionsordnung

Hiermit erkläre ich, **Luisa Karolina Maulitz,** an Eides statt, dass ich den wesentlichen Anteil an der Publikation:
Maulitz, L., Stickeler, E., Stickel, S., Habel, U., Tchaikovski, S. N., & Chechko, N.: Endometriosis, psychiatric comorbidities and neuroimaging: Estimating the odds of an endometriosis brain. *Frontiers in neuroendocrinology;* 2022, *65*, 100988,
geleistet habe.

Die Anteile an der Arbeit waren wie folgt:

	L. Maulitz	S. N. Tchaikovski	N. Chechko	U. Habel	S. Stickel	E. Stickeler	Summe (%)
Studienüberwachung		60	35	0	5	0	100
Studiendesign/ Konzeption	20	40	40	0	0	0	100
Systematische Datenerhebung/ Systematische Datenrecherche	100	0	0	0	0	0	100
Datenauswertung	100	0	0	0	0	0	100
Abstract-Screening	100	0	0	0	0	0	100
Volltext-Screening	100	0	0	0	0	0	100
Datenextraktion	100	0	0	0	0	0	100
Statistische Auswert.	100	0	0	0	0	0	100
Bereitstellung von Materialien/ Publikationskosten	0	0	0	50	0	50	100
Interpretation der Datenauswertung	80	10	10	0	0	0	100
Verfassung des Manuskripts	**100**	0	0	0	0	0	100
Korrektur des Manuskripts	0	35	35	10	10	10	100

Aus diesem wesentlichen Anteil ergibt sich selbstverständlich die Stellung als Erstautorin.

_____
Luisa Karolina Maulitz
Unterschrift der Doktorandin

Als Doktorvater bestätige ich die Angaben von Luisa Karolina Maulitz.

_____
Univ.-Prof. Dr. med. E. Stickeler
Unterschrift des Doktorvaters

Erklärung gemäß § 5 Abs. (1) und (2), und § 11 Abs. (3) 12. der Promotionsordnung

Hiermit erkläre ich, **Luisa Karolina Maulitz,** an Eides statt, dass ich den wesentlichen Anteil an der Publikation:
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geleistet habe.

Die Anteile an der Arbeit waren wie folgt:

	Luisa Maulitz	S. N. Tchaikovski	N. Chechko	A. Ignatov	S. Nehls	T. Kupec	A. T. Henn	E. Stickeler	Summe (%)
Studienüberwachung	0	80	0	0	0	0	0	20	100
Studiendesign/Konzeption		50	45	0	5	0	0	0	100
Untersuchung der Probanden	100	0	0	0	0	0	0	0	100
Datenerhebung	100	0	0	0	0	0	0	0	100
Datenauswertung	100	0	0	0	0	0	0	0	100
Durchführung der Experimente: MRT	90	0	0	0	10	0	0	0	100
Durchführung der Experimente: SCID	95	0	0	0	0	5	0	0	100
Durchführung der Experimente: Schmerzwahrnehmung	100	0	0	0	0	0	0	0	100
Statistische Auswert.	95	0	0	0	0	0	5	0	100
Bereitstellung von Materialien	0	50	25	0	0	0	0	25	100
Interpretation der Datenauswertung	80	20	0	0	0	0	0	0	100
Verfassung des Manuskripts	**100**	0	0	0	0	0	0	0	100
Korrektur des Manuskripts	0	55	5	5	10	5	10	10	100

Aus diesem wesentlichen Anteil ergibt sich selbstverständlich die Stellung als Erstautorin.

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Luisa Karolina Maulitz
Unterschrift der Doktorandin

Als Doktorvater bestätige ich die Angaben von Luisa Karolina Maulitz.

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Univ.-Prof. Dr. med. E. Stickeler
Unterschrift des Doktorvaters