Chapter 16
Neuroimaging Studies of Primary Dysmenorrhea

Intan Low, Shyh-Yuh Wei, Pin-Shiuan Lee, Wei-Chi Li, Lin-Chien Lee, Jen-Chuen Hsieh, and Li-Fen Chen

Abstract Primary dysmenorrhea (PDM), cyclic menstrual pain in the absence of pelvic anomalies, is one of the most common gynecological disorders in reproductive females. Classified as chronic pelvic pain syndrome, PDM encompasses recurrent spontaneous painful (“on”) and pain-free (“off”) states and is thus a good clinical model to study state- and trait-related changes of pain in the brain. In this chapter, we summarize state-of-the-art neuroimaging studies of primary dysmenorrhea from phenotype and endophenotype to genotype facets. Structural and functional brain alterations associated with primary dysmenorrhea are discussed.

I. Low
Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan
Integrated Brain Research Unit, Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan

S.-Y. Wei · W.-C. Li · L.-C. Lee
Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan

P.-S. Lee
Institute of Biomedical Informatics, National Yang-Ming University, Taipei, Taiwan

J.-C. Hsieh
Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan
Integrated Brain Research Unit, Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan
Brain Research Center, National Yang-Ming University, Taipei, Taiwan
e-mail: jchsieh@ym.edu.tw; jchsieh@vghtpe.gov.tw

L.-F. Chen
Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan
Integrated Brain Research Unit, Department of Medical Research, Taipei Veterans General Hospital, Taipei, Taiwan
Institute of Biomedical Informatics, National Yang-Ming University, Taipei, Taiwan
Brain Research Center, National Yang-Ming University, Taipei, Taiwan
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16.1 Prevalence, Clinical Diagnosis, and Psychological Features of Primary Dysmenorrhea

16.1.1 Importance of Primary Dysmenorrhea (PDM)

Primary dysmenorrhea (PDM) is menstrual pain in the absence of organic pelvic diseases [89]. It is the most prevalent gynecological problem affecting 90% of adolescent girls and more than 50% of menstruating women worldwide, with 10–20% of them experienced severe pain [10]. PDM often results in school or work absenteeism and casts a substantial economic burden on the society [33].

PDM is clinically diagnosed based on medical history and physical examination to exclude pelvic pathology (menstrual pain with pelvic pathology is classified as secondary dysmenorrhea) [60, 100]. It typically begins at or shortly (6–24 months) after menarche. The pain usually starts 1 or, at the earliest, 2 days before the start of the menstrual period and stops 1 or, at the latest, 2 days after menstrual bleeding starts, resulting in menstrual pain that typically lasts for 8–72 h [10, 34, 89]. The current most widely accepted pathogenesis of PDM is the overproduction of uterine prostaglandins, which causes myometrial hypercontractility and uterine vasoconstriction, leads to reduced uterine blood flow, and, ultimately, results in dysmenorrheic pain [34, 60].

PDM is formally coded and classified by International Association for Study of Pain (IASP) and World Health Organization (WHO):

1. 765.X8—under XXIII-15: Primary dysmenorrhea, Group XXIII: Chronic pelvic pain syndromes—“Gynecological System: Internal Pelvic Pain Syndromes” and Section F: “Visceral and Other Syndromes of the Trunk Apart from Spinal and Radicular Pain” in current IASP classification system of chronic pain by IASP
3. MG30.00: Chronic primary visceral pain and GA34.3: Dysmenorrhea under “Female pelvic pain associated with genital organs or menstrual cycle” in the current ICD-11 by WHO as a new diagnostic entity which is formerly neglected in etiologically defined categories [126]

PDM has been considered a genuine model of chronic pain for studying chronic recurrent pain because of its natural “on” (painful) and “off” (pain-free) states. PDM patients (PDMs) suffer from cyclic menstrual pain lasting for days during
each menstrual cycle for years [100]. Notably, dysmenorrhea often co-occurs with chronic pain conditions later in life, including irritable bowel syndrome, painful bladder syndrome, fibromyalgia, chronic headache, chronic low back pain, etc. [10] (further discussed in Sect. 16.3.1).

16.1.2 Quality of Life and Mood in PDM

Dysmenorrhea is associated with decreased self-rated overall health [7] and negative moods [39]. We recently reported that Taiwanese PDMs exhibited significantly lower physical and mental quality of life and higher levels of anxiety, depression, and pain catastrophizing than those of females without PDM [70]. Women with high level of pain catastrophizing may develop negative cognitive appraisal style, which may gradually lead to negative effects such as depression and anxiety and negative pain schema such as pain helplessness [101]. Such alterations sculptured by severe and long-term menstrual pain may ultimately influence women’s long-term health through pain chronification as other chronic diseases do.

16.1.3 Pain Sensitivity in PDM

Previous studies reported that Caucasian women with PDM might demonstrate increased pain sensitivity or central sensitization to experimental somatic [3, 5, 48, 51] and visceral stimuli [13] compared with those without PDM. However, no local or generalized hypersensitivity of superficial thermal pain was found in Taiwanese PDMs [70], indicating that different genetic constitutions (caused by ethnicity) may contribute to the diversity of the clinical manifestations of PDM.

16.2 Structural Brain Alterations in PDM

T1-weighted magnetic resonance imaging (MRI) provides a high-resolution contrast of soft tissues, such as gray matter and white matter in the brain. Structural brain alterations are often studied by measuring gray matter volume, white matter volume, cortical thickness, white matter microstructure, and fiber tract organization. Previous studies on chronic pain have reported reduced gray matter volume, reduced cortical thickness, and altered white matter microstructure in pain processing regions such as the cingulate cortex, insula, and thalamus [21, 117, 123]. Comparing with neuroimaging evidence from other chronic pain conditions, there are relatively few studies that demonstrate structural brain alterations in PDM. In this session, we introduce current findings of gray matter alterations [81, 129, 131] and white matter alterations [79, 80] in PDM.
When studying brain alterations, participants with brain anomalies or abnormalities, which might stem from abnormal development, injury, or disease, should be excluded from neuroimaging studies. It is noteworthy that there is a higher prevalence of incidental brain anatomy findings (normal variants) in PDMs, especially cavum septum pellucidum [73]. However, it is unlikely to link these incidental findings to developmental factors since, from organogenesis perspective, uterus and brain stem from different embryological origins [108]. Nevertheless, incidental findings in PDMs should be considered when interpreting future brain findings of PDM.

### 16.2.1 Gray Matter Alterations in PDM

A widely used technique for gray matter volume investigation is voxel-based morphometry (VBM). VBM is an automatic, unbiased, semiquantitative analysis technique and has become a standard whole-brain exploratory analysis procedure [49]. However, it measures cortical tissues collectively, which did not differentiate among other features, such as cortical thickness, cortical surface area, and cortical folding, for a better discriminative capability of anatomical boundaries [147].

Previous PDM studies using VBM analysis demonstrated that recurrent menstrual pain is associated not only with trait-related [129] but also state-related structural brain alterations [131]. Short-lasting cyclic menstrual pain changes the gray matter volumes in brain regions related to pain information processing and modulation (including somatosensory cortex, insula, and cingulate cortex), as well as in regions that regulate estrogen level (hypothalamus). PDMs showed decreased gray matter volume (hypotrophic changes) in the secondary somatosensory cortex (SII)/posterior insula, mid-anterior insula, and medial prefrontal cortex (mPFC). The SII/posterior insula and mid-anterior insula receive sensory input from visceral organs and play key roles in integrating sensory information with pain affect [31, 36]. The posterior insula responses to viscerosensory afferents and is sensitive to physiological stress [107]. The mPFC exerts massive visceromotor control outputs and is largely involved in subjective affective experience [63]. These decreases of gray matter volume might be the consequence of compensatory inhibitory responses toward excessive cyclic viscerosensory input of menstrual pain [104, 129, 131].

In contrast, PDMs showed increased gray matter volume (hypertrophic changes) in the hypothalamus, hippocampus, periaqueductal gray (PAG), and anterior cingulate cortex (ACC). The hypothalamus is involved in menstrual pain through several potential pathways [129], including the hypothalamic–pituitary–gonadal (HPG) axis, the hypothalamic–pituitary–adrenal (HPA) axis, and the spino-bulbo-spinal loop. First, the hypothalamus responds to elevated estrogen levels through the HPG axis [146]. Estrogen is essential in regulating the synthesis of uterine prostaglandins in both qualitative and quantitative ways [53]. Periodically increased estrogen levels result in elevated levels of prostaglandins, which together contribute to the overproduction of prostaglandins, causing menstrual pain in PDMs [33, 60].
Second, hypothalamus and hippocampus are key regions in the HPA stress regulation system. PDM is thought to be intensified by heightened emotional stress [138] that is generated by abnormal hippocampal feedback to the hypothalamus [61, 90, 133]. Third, dysfunction of the spino-bulbo-spinal loop and its cortical feedback (including the hypothalamus, PAG, amygdala, hippocampus, ACC) may lead to enhanced negative mood and emotions associated with pain perception [122]. In short, gray matter volume increases in PDMs may underpin reactive pain modulation and the regulation of endocrine function.

On the other hand, using cortical thickness measurement, Liu et al. [81] found that PDMs had increased global mean cortical thickness and regional cortical thickness compared to healthy female controls. These cortical regions included the orbitofrontal cortex, superior temporal cortex, precuneus, posterior cingulate cortex, primary and secondary somatosensory cortex, insula, and parahippocampus. Their findings were similar to previous VBM studies reported [129, 131]. All these findings demonstrate that protracted nociceptive input could result in a combination of decreased pain inhibition or increased pain facilitation in PDMs.

16.2.2 White Matter Microstructural Alterations in PDM

Diffusion-weighted MRI has encouraged the analysis for microstructural properties of white matter. Diffusion tensor imaging (DTI) is a promising technique to non-invasively quantify the white matter tract organization and microstructural feature in human brains [8]. Fractional anisotropy, mean diffusivity, radial diffusivity, and axial diffusivity are common DTI measurements [80]. Fractional anisotropy estimates the directional preference of molecular diffusion of water and reflects white matter integrity. Mean diffusivity estimates molecular diffusion rate and may reflect the inflammatory swelling. Radial diffusivity estimates the diffusion rate in the transverse direction and axial diffusivity estimates the diffusion rate along the main tract; they may reflect changes in membrane permeability and myelination [1, 119]. These directional estimates endow us with the possibilities of performing diffusion tractography to trace the pathways of underlying fiber bundles.

Contradictory findings of increased or decreased fractional anisotropy in PDM have been reported, while consistent findings of mean diffusivity and radial diffusivity are reported by Liu et al. [80] and Dun et al. [40]. Liu et al. [79] focused on white matter microarchitecture alteration in the cingulum bundle using tract-based analysis method and found decreased FA in the dorsal-posterior and parahippocampal section. Posterior cingulum cortex has a pivotal role in the default mode network (DMN) [14]. Several studies reported abnormal morphology or function of DMN in PDMs [129, 139, 142], which may suggest maladaptive neuroplasticity of the endogenous pain control systems.

Tract-based spatial statistics (TBSS) [118] is a skeleton projection algorithm that could mainly detect the deficits in white matter tract. Previous studies using TBSS demonstrated white matter microstructural abnormalities in PDMs [40, 80], including
alterations in the corpus callosum, longitudinal fasciculus, corona radiate, internal capsule, fornix, thalamic radiation, and external capsule.

Corpus callosum, which is the brain’s core commissural white matter bundle, plays an essential role in the interhemispheric communication [113]. Abnormal interhemispheric transfer in the corpus callosum may result in augmented pain perception. White matter microstructural anomalies in the corpus callosum may disrupt structural connectivity and may affect PDMs in integrating pain modulation and sensory information [80].

Longitudinal fasciculus connects the anterior to posterior cerebral parts, including the frontal, parietal, and occipital cortices [128]. Alterations in the superior longitudinal fasciculus have been reported in pain-related disorders [37, 75] and PDM [80], implicating disrupted functions in the affective and cognitive processing.

Internal capsule locates at the inferior medial part of each hemisphere. It consists of ascending and descending fiber tracts that convey information between cortical and subcortical regions and the spinal column. External capsule contains corticocortical association fibers and conveys information pertaining to the emotional component of pain perception [75]. White matter microstructure alterations in the internal and external capsules might implicate abnormal sensation and pain arising from the uterine, which could further cause abnormal hypometabolism in the somatosensory and emotional regions [130].

Corona radiata is the most prominent projection fibers of the cerebral cortex. It is a white matter sheet containing both ascending and descending axons. Anterior corona radiata passes through the limbic-thalamo-cortical circuitry and is implicated in top-down emotional regulation [109]. Tu et al. [130] suggested that the disinhibition of thalamo-orbitofrontal-prefrontal network in PDM might increase negative emotion and thus might result in pain generation and heightened pain sensitivity.

In summary, both gray and white matter abnormalities in primary dysmenorrhea implicate that PDM manifests characteristics common to chronic pain that may pose impacts on functional neuroplasticity.

### 16.3 Functional Brain Alterations in PDM

#### 16.3.1 Resting-State fMRI Studies in PDM

Among all the neuroimaging techniques, resting-state functional magnetic resonance imaging (rs-fMRI) is widely used to study brain function in the absence of explicit input or output [12, 44]. The rs-fMRI measures blood oxygen level-dependent (BOLD) signals during rest and noninvasively reveals the manifestation of spontaneous neuronal activity, allowing us to study the intrinsic functional connectivity of the brain [44]. In chronic pain patients, such task-free brain activity reflects a combination of spontaneous thought processes and ongoing neural and
physiological maintenance processes involved in ongoing pain [32, 64]. Variability in brain activity can provide insights into brain health, pain sensitivity, and the capacity for brain plasticity [105].

To further unravel functional brain networks, resting-state functional connectivity (FC) has been developed by measuring the temporal correlation of low-frequency spontaneous fluctuations in the BOLD signals between different brain regions [12]. Resting-state FC may reflect brain state of readiness to engineer an instant mind operation [46], system memory out of intensive short-term training [72], and sustained long-term learning and plasticity [76, 124]. Functional connectivity studies have also revealed abnormal brain networks (brain states) in various chronic pain conditions, shedding light on the pathophysiological mechanisms underlying different facets of pain chronification, as well as the neural bases for neurocognitive conditions (mind states) of chronic pain [6, 27, 58, 65, 85, 94].

Based on the established functions of particular brain regions (regions of interest; ROIs), seed-based functional connectivity is developed to calculate the temporal correlations between neural signals in an ROI (the “seed”) and those in all other regions [44]. The descending pain modulation system (DPMS) consists of neural substrates and pathways from the cerebral cortex to the spinal cord and modulates different dimensions of pain, including sensation, cognition, and emotions [17]. Periaqueductal gray (PAG) is one of the most critical neural substrates of the DPMS, functioning as its critical hub [20]. Based on the established engagement of PAG in the overall brain alterations associated with PDM [129], we focused on the PAG and employed a seed-based resting-state FC approach through fMRI to address the functional dynamics of the PAG-seeded FCs in the DPMS.

The neural networks between the PAG and pain-related brain regions have been revealed in studies of brain anatomy [20], resting-state fMRI [62], and diffusion tensor imaging [77]. PAG connects directly and indirectly with rostral ventromedial medulla (RVM) to act on pain facilitation (ON cells) and pain inhibition (OFF cells) in pain downstream transmission [95]. Homeostatic regulation shifts dynamically between pain facilitation and inhibition, resulting in either augmented or diminished central sensitization of pain [57] and leads to inappropriate inhibition or facilitation of ascending pain signals [35]. This feature is shared among many chronic pain disorders [11, 15, 114, 120]. On the other hand, DPMS might be pre-injured and confer a vulnerability toward chronic pain [35].

We recently reported that PDMs demonstrated maladaptive functional hypo-connectivity (hypo-FC) between PAG and many critical regions of the DPMS but adaptive/reactive functional hyper-connectivity (hyper-FC) between PAG and the sensorimotor cortex [139]. Furthermore, the PAG-FCs demonstrated predictive values for the overall quality of life in PDMs. The higher the correlation strength of the PAG-sensorimotor FC, PAG-ventrolateral prefrontal cortex FC, and PAG-posterior parietal cortex (PPC) FC, the lower the physical well-being. Maladaptive FCs in the DPMS, including FCs of the PAG-mPFC and PAG-supplementary motor area (PAG-SMA), found in young PDMs may underpin the central susceptibility to the development of chronic pain disorders later in life [139]. PAG-mPFC hypo-FC is
common in functional pain disorders, while PAG-SMA FC alteration is shared by chronic pelvic pain syndromes [67].

Maladaptive PAG-seeded functional connectivity in the DPMS altered by long-term menstrual pain may be the cause that dysmenorrhea often co-occurs with many functional disorders and chronic pain conditions later in life. These co-occurrences include painful bladder syndrome [26], irritable bowel syndrome [2], fibromyalgia [48], temporomandibular joint disease, chronic fatigue syndrome, chronic headache, low back pain, and many others [10]. Notably, all these functional pain disorders have pronounced female predominance [92], and their highest prevalence rates usually occur after the age of 30 [84]. In contrast, the prevalence of PDM peaks much younger [121]; newly diagnosed PDM usually occurs before the age of 30 in Taiwanese females [96]. The high comorbidity of PDM with many chronic pain conditions later in life suggests that possible maladaptive functionality of DPMS may occur in young PDMs, predisposing them vulnerable to functional pain disorders. This point is of particular importance because pain and stress early in life can predict a reduced quality of life and severe or chronic pain later in life [10]; furthermore, early life injury (i.e., PDM) may create an imbalance in the DPMS [35].

Our findings of alterations in the PAG-seeded FC tie together previous reports of altered metabolism and gray matter structure in the DPMS and are in line with the results of our structural neuroimaging studies of PDM (see Sect. 16.2). We previously reported trait-related decrease in regional gray matter volume in the DMN (including mPFC and precuneus) and PPC [129] and state-related increase in regional gray matter volume in the primary somatosensory cortex in PDM [131]. In seed-based FC, we observed trait-related hypo-FCs of PAG-DMN and PAG-PPC and state-related hyper-FC of PAG-sensorimotor FC in PDM. Therefore, structural changes may be coupled with alterations in the resting network organization in corresponding brain regions.

16.3.2 Resting-State MEG Studies in PDM

Magnetoencephalography (MEG) is a noninvasive neurophysiological technique that uses highly sensitive sensor arrays to directly capture tiny changes in the magnetic fields produced by small changes in the brain’s electrical activity [54, 84]. MEG possesses superior temporal resolution and good spatial resolution [54], which complements the coarse temporal resolution of fMRI and coarse spatial resolution of electroencephalography (EEG) [4]. Thus, MEG is an excellent tool to study the regularity and irregularity of brain signals, such as brain rhythms and brain dynamics, respectively. In addition, various source estimation methods can be applied to investigate neural sources in the brain, such as dipole fitting, minimum current estimation, and beamformer techniques. Evaluating different facets of central changes in PDMs using various signal analysis techniques helps us to advance our understanding of chronic pain and further provides clinically useful information and improves diagnostic utility of chronic pain.
16.3.2.1 Resting-State Brain Rhythms Alterations in PDM

Neural synchronization is temporally precise interactions between neural assemblies, telling us how regular neuronal populations synchronize rhythmically at distinct frequency bands each with specific functions [87]. To further understand pain-related rhythms in PDM, neural oscillations indexes such as phase synchronization [42, 111] and cross-frequency coupling [19, 59] are considered.

The phase of neural oscillations at a given frequency band reflects a network’s excitability due to cyclic fluctuations and is affected by the precise discharge time of neurons [42], offering insights to link putative neural mechanisms to sensory perception [16, 132]. Phase synchronization is considered to promote neural communication and neural plasticity [42].

The analysis of brain rhythms and oscillations has been applied to localize pain-related activity in narrow or wide frequency bands during resting state [25, 66, 71, 93]. Spontaneous low (delta, theta, and alpha) and high (beta and gamma) frequency oscillations have been associated with the sensory, affective, and evaluative representations of pain processing [97–99]. Recently, we used a beamformer method [23] to localize theta activity during painful and pain-free states in PDMs [71]. We observed elevated theta activity in regions related to sensory and emotional processing, which might be related to thalamocortical dysrhythmia in chronic pain [110, 112, 136]. Our findings suggested the role of theta oscillation in the encoding of complicated processes related to perception and context of menstrual pain experience [71].

On the other hand, cross-frequency coupling is calculated as the statistical relationship between oscillatory activities across two different frequency bands. Phase-amplitude coupling (PAC), in particular, may be the most frequently reported cross-frequency coupling in pain studies. PAC reflects the interaction between phase and amplitude, where the envelope of the faster oscillations is modulated by the phase of the slower oscillations [19, 22, 78].

Although currently there are no studies of cross-frequency coupling in PDM, Liu et al. [78] demonstrated that during painful laser stimulations, increased gamma local field potentials in the right amygdala and hippocampal significantly coupled with the phases of theta and alpha oscillations. Hippocampus and amygdala, two significant elements in the limbic structure, are fundamental in the generation of emotion and emotional memory [69, 106]. Thus, gamma low-frequency coupling is speculated to be a basic mechanism of integrating the sensory and affective dimensions of pain [78].

Overall, analyzing brain rhythms is a straightforward and objective tool to study the mechanisms involved in menstrual pain and the encoding of menstrual pain experience. Further studies utilizing quantitative analysis of oscillations and synchrony in PDM are invited.
16.3.2.2 Resting-State Brain Dynamics Alterations in PDM

The brain is a complex system encompassing both regular and irregular neural activities. The temporal irregularity and unpredictability of neural signals at multiple temporal scales can be regarded as neural complexity, which may reflect the adaptability/flexibility of the nervous system and the information processing between neurons [86, 125, 137]. Measuring nonlinear temporal variability of brain signals using entropy measures would provide a useful metric of brain dynamics [47], which would fundamentally complement the information revealed by spectral-based analysis.

Multiscale entropy (MSE) [28, 29] measures the irregularity of time-varying signals by calculating sample entropy [103] over multiple time scales. Loss of complexity is often reported in neuropsychiatric diseased and aged groups; increased complexity has been seen in healthy and recovery conditions [52, 74, 143]. Recently, MSE analysis has also been applied to pain [82, 116, 134] and PDM studies [66, 83].

We recently developed a model to predict subjective spontaneous pain level by decoding resting-state MEG signals of PDMs during painful state (menstruation) [66]. We found that brain complexities in the precuneus and posterior cingulate cortex, which are key regions of the DMN, were the most selected features in predicting subjective spontaneous pain level. In addition, we compared the brain complexity during pain-free state in PDMs and healthy female controls using resting-state MEG signals to investigate trait-related changes in neural adaptability after long-term menstrual pain [83]. PDMs demonstrated loss of complexity in pain-related sensory, affective, and evaluative regions. General loss of brain complexity in pain-related regions revealed by nonlinear dynamical analysis might suggest a loss of neural adaptability and efficiency [47] in response to chronic recurrent pain and might correspond to low-frequency alterations in chronic pain [83].

To sum up, changes in resting-state MEG activity in PDMs [66, 71, 83] may reveal abnormalities of the underlying neurophysiological mechanisms involved in the sensory, cognition, and emotion components of long-term menstrual pain experience. Brain rhythms alterations in PDMs might have resulted from alterations in regional gray matter volume or cortical thickness [81, 129, 131], white matter structural connectivity [79, 80], and functional connectivity [139, 142] within the pain modulatory system. Accordingly, these findings support the idea that there are alterations in multiple interactively connected networks that receive inputs from various parallel nociceptive pathways, including the sensorimotor network, default mode network, salience network, and limbic regions.

16.4 Interactions of Genotype Polymorphisms and Long-Term Menstrual Pain

The perception of pain and the clinical response to analgesics vary among people; genetic factors, at least partially, may explain the variability in the experience of pain [18]. Therefore, genetic testing in pain may enhance the selection, dosing, and
evaluation of medical treatment [127]. Recent evidence suggests a role of single-nucleotide polymorphism (SNP), a substitution at a specific position in the genome, in the serotoninergic, dopaminergic and catecholaminergic systems [18]. Persistent alteration in histone methylation at the promoter region of brain-derived neurotrophic factor (BDNF) has been linked to depression and could also be relevant in chronic pain [30]. In the same vein, studies have revealed a wide variety of risk alleles for chronic pain, including mu-opioid receptor (OPRM1), catechol-O-methyltransferase (COMT), serotonin receptor 2A (5HTR2A), and solute carrier family 6, member 4 (SLC6A4; serotonin transporter) [91].

Imaging genetics, using neuroimaging as endophenotypic assays to evaluate genetic variations [55], is a new strategy in brain science developed during the past decade. Genetic impact on the brain endophenotype (intermediate phenotype) can be more significant than its impact on behavioral phenotype [102]. Thus, brain imaging bridges the mechanistic gap between genotype and phenotype [35]. Furthermore, only a proportion of patients with acute pain go on to develop chronic pain; both genotype (innate mechanisms) and disease at critical developmental periods (acquired mechanisms) are crucial risk factors [35]. In PDM, maladaptive PAG-seeded FC was found in the DPMS that may eventually contribute to the comorbidity of various chronic pain disorders later in life; we also reported that such maladaptive neuromodulation of DPMS might have genetic attributions [140, 141].

16.4.1 The BDNF Val66Met Polymorphisms Influence the Functional Connectivity Dynamics of the DPMS

BDNF modulates the formation, maturation, and plasticity of neuronal synapses [50], including those at the spinal and supraspinal levels of pain circuitry [88]. Therefore, BDNF is crucial in central sensitization and chronic pain [68]. The BDNF Val66Met (rs6265) is a SNP which leads to valine (Val)-to-methionine (Met) substitution at codon 66. This functional polymorphism has been shown to reduce activity-dependent BDNF secretion [24, 41] and influences cortical pain processing [38, 135].

The BDNF Val66Met polymorphism is associated with diverse functional expressions of the DPMS in healthy subjects. Individuals with different BDNF Val66Met genotypes demonstrate different functional dynamics of the DPMS upon long-term recurrent menstrual pain [140]. The Val/Val PDMs mainly engage the ascending pain-sensory system (adaptive neuroplasticity), while the Met/Met PDMs exhibit significant PAG-limbic structure FCs, indicating a predisposition of pain chronicity (maladaptive neuroplasticity) [56].

Our reasoning is corroborated by the anatomical and physiological evidence in the PAG. BDNF-containing projecting neurons, especially those in the ventrolateral PAG, project to RVM and release BDNF that might participate in the descending pain modulation [145]. Analgesic effect has been observed by infusing BDNF into rats’ PAG-dorsal raphe [45]. In addition, healthy subjects with Met alleles showed a less progressive reduction of ERP responses to experimental pain [38], whereas low
back pain patients with Met alleles showed heightened sensitivity to experimental pain [135]. This effect may occur through neural plasticity affected by neurotrophin polymorphism or through direct neurotransmitter-like effect of BDNF [38]. Moreover, we had previously described the possible genetic association of BDNF Val66Met polymorphism with the susceptibility to PDM [70].

16.4.2 The OPRM1 A118G Polymorphisms Are Associated with the DPMS

On the other hand, OPRM1 remarkably mediates the analgesic effects of opioids in the central nervous system [43]. The OPRM1 A118G (rs1799971) is a SNP which leads to an adenine (A)-to-guanine (G) substitution at codon118 in the human OPRM1 gene. It is associated with reduced OPRM1 gene expression [148], heightened pain sensitivity [144], and increased analgesics consumption [115].

The OPRM1 A118G polymorphism influences the functional connectivity dynamics in the DPMS during menstrual pain (but not during pain-free state) in PDMs, suggesting that menstrual pain experience might be an epigenetic factor that interacts with genetic polymorphism [141]. The AA homozygous PDMs exhibited an active cortical modulation, while G-carriers PDMs showed decreased functional connectivity and dysregulation in the DPMS.

In summary, genetic polymorphisms modify the functional dynamics of DPMS and may underlie altered pain processing or predict differential efficacy of analgesics. Indeed, PAG, the critical hub in the DPMS, is enriched with opioidergic neurons [43], and its ventrolateral subregion is vital for opioid-mediated analgesia [9]. The interactions between genetic polymorphism and DPMS are plausible neurological mechanisms underlying intersubject variations in pain experience and may eventually predispose PDMs to the vulnerability of chronic pain conditions.

16.5 Conclusions

In this chapter, we reviewed neuroimaging studies in females with primary dysmenorrhea. Structural brain alterations in PDM include alterations in gray matter volume, cortical thickness, and white matter microstructure. Functional brain alterations in PDM include alterations in resting-state functional connectivity, resting-state brain rhythms, and resting-state brain dynamics. Genotype polymorphisms currently reported in PDM include the BDNF Val66Met polymorphism and the OPRM1 A118G polymorphism. These alterations highlight the state- and trait-related assaults of long-term menstrual pain experience on our most complex organ, the brain. We suggest the early diagnosis of PDM and appropriate treatment or pain medication to prevent pain chronification that predisposes PDMs to the development of chronic pain disorders later in life.
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