Chapter II

Functional and Structural Brain Alterations Associated with Menstrual Pain

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Abstract

Dysmenorrhea is a widely presented gynecological disorder for women in the childbearing age. Females with dysmenorrhea suffer from

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disabling, cramping pain emanating from the lower abdomen with the onset of menstrual flow and the pain persists for 24–72 hours. Recent studies further disclosed that central sensitization exists in dysmenorrhea as hyperalgesia spans different spinal segments and multiple tissue systems (e.g., skin and muscle) and extends to non-referred pain areas during the menstrual phase. Moreover, menstrual pain is associated with functional and structural alterations in highly specified regions involved in pain transmission and modulation, generation of the affective experience, and regulation of endocrine function. The adaptive and mal-adaptive changes in the brain may be engaged simultaneously and dynamically and that some of these regions may underpin the hyperalgesia in dysmenorrhea.

The functional and structural brain alterations may either be either state-related or trait-related. Where state-related changes are associated with the presence of menstrual pain, trait-related changes exist even in the absence of symptoms.

When comparing pain and pain-free states, the rapid state-related structural changes in several regions correlating with the severity of the menstrual pain experience, suggesting that these changes are primary changes rather than epiphenomena. Some of the observed state-related structural alterations even persisted into the pain-free state indicating an accumulating effect of the cyclic menstrual pain. This notion is supported by a correlation of gray matter volume in these regions with menstrual pain duration.

More specifically, regions involved in pain modulation and affect regulation exhibited hypertrophy and regions associated with pain transmission showed atrophic changes.

Using positron emission topography to study state-related changes in glucose metabolism, the alterations in central processing of menstrual pain suggest that a disinhibition of inhibition of a thalamo-orbitofrontal-prefrontal network may promote central sensitization during menstruation. On the other hand, reduced metabolism was also found in sensory-discriminative areas, indicating a down regulation in pain transmission pathways.

These findings are congruent with the structural brain alterations observed in dysmenorrhea. Overall, these results indicate that the adolescent brain is vulnerable to menstrual pain. Considering the high prevalence rate of dysmenorrhea and the early onset of primary dysmenorrhea, these findings mandate a great demand to revisit dysmenorrhea regarding its impact on the brain and other clinical pain conditions. Like the migraine, dysmenorrhea might be considered a chronic disease with episodic features but largely confined to the menstrual phase.
Section I. Introduction

Dysmenorrhea is the most common gynecological disorder for women in the reproductive age. Dysmenorrhea patients suffer from disabling cramping pain emanating from the lower abdomen. It has been estimated that absenteeism due to severe dysmenorrhea may cause about 600 million lost working hours or 2 billion dollars annually in the United States [1]. Clinically, dysmenorrhea can be categorized as Primary and Secondary [2]. Primary dysmenorrhea refers to menstrual pain without macroscopic pelvic abnormality. Secondary dysmenorrhea refers to menstrual pain associated with pelvic abnormality (i.e., endometriosis) and occurs less frequently than primary dysmenorrhea [2].

In this chapter, we mainly focus on supraspinal changes associated with dysmenorrhea. Initially, we give a short review of the characteristics of dysmenorrhea and what is known about the pathophysiological mechanisms. Second, we briefly introduce the current understanding of how pain is processed in the brain. We then move on to discuss our findings regarding the impact of dysmenorrhea on the brain. Finally, we discuss the possible implications of these findings and their clinical relevance.

1.1. Clinical Features

Individuals with dysmenorrhea suffer from fluctuating, spasmodic menstrual cramping pain emanating from the suprapubic area. The cramping pain typically starts a few hours before or with onset of the menstrual flow, and last for 24 to 72 hours in primary dysmenorrhea [3]. The menstrual pain may radiate into the inner aspects of the thighs or lumbosacral region. Backache, nausea, vomiting, and diarrhea may also accompany dysmenorrhea [4]. These symptoms may be of such incapacitating severity that absence from school or work is required for days. Typically, primary dysmenorrhea presents with or shortly (within 6 to 12 months) after menarche. Since primary dysmenorrhea only presents in ovulatory cycles, it is less common during early adolescence with anovulatory menstrual cycles [2], and is most prevalent in the early 20's [5]. The typical history of suprapubic pain associated with the menstrual flow beginning in adolescence and the absence of any positive findings in the physical examination are key diagnostic features [6]. However, there is no specific laboratory test for primary dysmenorrhea. In contrast,
secondary dysmenorrhea is associated with observable pelvic abnormality, it presents at a later stage (years after the menarche), and may persist for a prolonged period of time [3].

1.2. Prevalence

Since the majority of dysmenorrhea in adolescents is primary [2], the epidemiology may mainly reflect the prevalence rate of primary dysmenorrhea. In the western society, an investigation in United States including 2,699 menarcheal adolescents (aged 12 to 17 years) revealed that dysmenorrhea was present in 59.7% of the study population, and 14% frequently missed school because of dysmenorrhea [7]. Another study of 1,546 menstruating Canadian women (aged 18 years and above) also found that 60% had dysmenorrhea, and 17% of them reported absenteeism from school or work due to dysmenorrhea [8]. Eighty percent of 388 Australian adolescents (aged 17 to 18 years) also reported experiencing dysmenorrhea and 53% of them reported limitation of activities [9]. Fifty-six percent of 4,992 Italian females (aged 13 to 21 years) report some degree of menstrual pain and 6.2% of these subjects were are limiting their daily activity by severe dysmenorrhea [10]. In Asia, a large-scale epidemiological study of 5,561 Singaporean female adolescents (aged 12 to 19 years) reported that 83.2% of the subjects experienced dysmenorrhea, and 24% reported school absenteeism owing to it [11]. An investigation in Malaysia among 1,075 menarcheal girls (aged 13 to 19 years) revealed that 74.5% had dysmenorrhea while 21.5% of them considered dysmenorrhea to be a leading reason to miss school [12]. In Japan and Korea, two recent studies included 1,431 Japanese and 538 Korean female adolescents (aged 16 to 18 years in Japan and 14 to 18 years in Korea) showed 85% and 82% of subjects experiencing dysmenorrhea, respectively [13, 14].

The prevalence rate of dysmenorrhea around the world is summarized in Table 1. It is noteworthy to mention that the severity of dysmenorrhea may be influenced by ethnic factors. An early study in the United States reported that the subgroups of African-American and Caucasian adolescents had similar prevalence rates of dysmenorrhea, but the former had nearly double the rate of school absenteeism due to menstrual pain (African-American: 23.6%, Caucasian: 12.3%) [7]. A study on Hispanic adolescents in the United State reported that the rate of severe menstrual pain was three times higher than the previously mentioned investigation (Hispanic: 42%, African-American and Caucasian: 14%) [7, 15]. In Asia, a recent study on menarcheal girls in
Malaysia reported a significant difference in the prevalence rate of dysmenorrhea among Malaysian (79.7%), Chinese (69.8%), and Indian (82.4%) subgroups [12]. Thus, ethnic factors need to be considered in the study of dysmenorrhea.

Table 1. Studies of Prevalence Rate of Dysmenorrhea in Different Countries

<table>
<thead>
<tr>
<th>Author</th>
<th>Pub. year</th>
<th>Sample size</th>
<th>Age</th>
<th>Prevalence</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grandi et al. [115]</td>
<td>2012</td>
<td>408</td>
<td>19-25</td>
<td>81.4%</td>
<td>Italy</td>
</tr>
<tr>
<td>Gumanga and Kwame-Aryee [116]</td>
<td>2012</td>
<td>456</td>
<td>14-19</td>
<td>74.4%</td>
<td>Ghana</td>
</tr>
<tr>
<td>Kariot et al. [117]</td>
<td>2012</td>
<td>352</td>
<td>18-26</td>
<td>38.1%</td>
<td>Lebanon</td>
</tr>
<tr>
<td>Kitamura et al. [13]</td>
<td>2012</td>
<td>1431</td>
<td>16-18</td>
<td>85%</td>
<td>Japan</td>
</tr>
<tr>
<td>Rigon et al. [10]</td>
<td>2012</td>
<td>4992</td>
<td>13-21</td>
<td>56%</td>
<td>Italy</td>
</tr>
<tr>
<td>Santina et al. [118]</td>
<td>2012</td>
<td>389</td>
<td>13-19</td>
<td>74.3%</td>
<td>Lebanon</td>
</tr>
<tr>
<td>Lee et al. [14]</td>
<td>2011</td>
<td>538</td>
<td>14-18</td>
<td>82%</td>
<td>Korea</td>
</tr>
<tr>
<td>Muhammad et al. [119]</td>
<td>2011</td>
<td>900</td>
<td>18-59</td>
<td>55.3%</td>
<td>Egypt</td>
</tr>
<tr>
<td>Omidvar and Begum [120]</td>
<td>2011</td>
<td>194</td>
<td>18-27</td>
<td>78.2%</td>
<td>India</td>
</tr>
<tr>
<td>Tavallaee et al. [121]</td>
<td>2011</td>
<td>381</td>
<td>16-56</td>
<td>90%</td>
<td>Iran</td>
</tr>
<tr>
<td>Wong [122]</td>
<td>2011</td>
<td>1295</td>
<td>13-19</td>
<td>76%</td>
<td>Malaysia</td>
</tr>
<tr>
<td>Agarwal and Agarwal [123]</td>
<td>2010</td>
<td>970</td>
<td>15-20</td>
<td>79.67%</td>
<td>India</td>
</tr>
<tr>
<td>Al-Kindi and Al-Bulushi [124]</td>
<td>2010</td>
<td>404</td>
<td>15-23</td>
<td>94%</td>
<td>Oman</td>
</tr>
<tr>
<td>Eryilmaz et al. [125]</td>
<td>2010</td>
<td>1951</td>
<td>13-18</td>
<td>68.1-72.2%</td>
<td>Turkey</td>
</tr>
<tr>
<td>Ortiz [126]</td>
<td>2010</td>
<td>1539</td>
<td>17-35</td>
<td>62.4%</td>
<td>Mexico</td>
</tr>
<tr>
<td>Parker et al. [127]</td>
<td>2010</td>
<td>1051</td>
<td>15-19</td>
<td>93.0%</td>
<td>Australia</td>
</tr>
<tr>
<td>Wong and Khoo [12]</td>
<td>2010</td>
<td>1092</td>
<td>13-19</td>
<td>74.5%</td>
<td>Malaysia</td>
</tr>
<tr>
<td>Unsai et al. [128]</td>
<td>2010</td>
<td>623</td>
<td>17-30</td>
<td>72.7%</td>
<td>Turkey</td>
</tr>
<tr>
<td>Chan et al. [129]</td>
<td>2009</td>
<td>5609</td>
<td>13-18</td>
<td>68.7%</td>
<td>Hong Kong</td>
</tr>
<tr>
<td>Fawole et al. [130]</td>
<td>2009</td>
<td>1213</td>
<td>9-23</td>
<td>72.7%</td>
<td>Nigeria</td>
</tr>
<tr>
<td>Yamamoto et al. [131]</td>
<td>2009</td>
<td>221</td>
<td>18-25</td>
<td>79.0%</td>
<td>Japan</td>
</tr>
<tr>
<td>Zegeye et al. [132]</td>
<td>2009</td>
<td>612</td>
<td>14-19</td>
<td>72.0%</td>
<td>Ethiopia</td>
</tr>
<tr>
<td>Pitts et al. [133]</td>
<td>2008</td>
<td>1983</td>
<td>16-49</td>
<td>71.7%</td>
<td>Australian</td>
</tr>
</tbody>
</table>
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Pub. year</th>
<th>Sample size</th>
<th>Age</th>
<th>Prevalence</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharma et al. [134]</td>
<td>2008</td>
<td>198</td>
<td>13-19</td>
<td>67.2%</td>
<td>India</td>
</tr>
<tr>
<td>Ortiz et al. [135]</td>
<td>2007</td>
<td>285</td>
<td>17-33</td>
<td>67.0%</td>
<td>Mexico</td>
</tr>
<tr>
<td>Banikarim et al. [15]</td>
<td>2000</td>
<td>706</td>
<td>15-18</td>
<td>85.0%</td>
<td>United States</td>
</tr>
<tr>
<td>Hillen et al. [9]</td>
<td>1999</td>
<td>384</td>
<td>15-17</td>
<td>80.0%</td>
<td>Australia</td>
</tr>
<tr>
<td>Gürel and Gürel [136]</td>
<td>1998</td>
<td>235</td>
<td>18-56</td>
<td>57.0%</td>
<td>Turkey</td>
</tr>
<tr>
<td>Harlow and Park [137]</td>
<td>1996</td>
<td>165</td>
<td>17-19</td>
<td>71.6%</td>
<td>United States</td>
</tr>
<tr>
<td>Jamieson and Steege [138]</td>
<td>1996</td>
<td>533</td>
<td>18-45</td>
<td>90.0%</td>
<td>United States</td>
</tr>
<tr>
<td>Ng et al. [139]</td>
<td>1992</td>
<td>415</td>
<td>15-54</td>
<td>51.3%</td>
<td>Singapore</td>
</tr>
<tr>
<td>Sundell et al. [140]</td>
<td>1990</td>
<td>489</td>
<td>24</td>
<td>67.0%</td>
<td>Sweden</td>
</tr>
<tr>
<td>Thomas et al. [141]</td>
<td>1990</td>
<td>768</td>
<td>15-34</td>
<td>72.3%</td>
<td>Nigeria</td>
</tr>
<tr>
<td>Pullon et al. [142]</td>
<td>1988</td>
<td>1826</td>
<td>16-54</td>
<td>53.0%</td>
<td>New Zealand</td>
</tr>
<tr>
<td>Andersch and Milsom [143]</td>
<td>1982</td>
<td>596</td>
<td>19</td>
<td>72.4%</td>
<td>Sweden</td>
</tr>
<tr>
<td>Klein and Litt [7]</td>
<td>1981</td>
<td>2699</td>
<td>12-17</td>
<td>59.7%</td>
<td>United States</td>
</tr>
</tbody>
</table>

Note: These studies were found by searching PubMed using “dysmenorrhea” and “prevalence” as keywords at the end of September, 2012. The search resulted in 561 studies. We excluded intervention studies, studies which did not report the prevalence rate of dysmenorrhea, and review articles. Thirty-seven studies were left and listed in the table. Studies are sorted chronologically and then in alphabetical order of author’s name.

1.3. Comorbidities

Clinically, dysmenorrhea is often comorbid with other idiopathic pain disorders. Irritable bowel syndrome (IBS) and fibromyalgia are two pain conditions with central sensitization [16, 17] that have a higher prevalence rate in females [18, 19] and are often comorbid with dysmenorrhea [20]. Furthermore, IBS patients have more severe clinical symptoms with concomitant dysmenorrhea than with IBS alone [21], and the treatment of dysmenorrhea can improve the symptoms of IBS [22].
A recent study further suggests that menstrual pain is associated with the possibility of having premenstrual dysphoric disorder [23], the most severe form of premenstrual symptoms. Finally, there are also indications that primary dysmenorrhea is associated with elevated state anxiety levels during menstruation [24, 25].

1.4. Pathophysiology

The etiology of primary dysmenorrhea has not been fully elucidated. The local inflammatory environment of the menstruating uterus has been suggested as the primary mechanism, but sensitization in the central nervous system may also play a role [3]. Peripherally, primary dysmenorrhea has been suggested to be a sex-hormone related disorder accompanied by a decrease of progesterone before menstruation [2]. The decline of uterine progesterone levels in the late luteal phase results in an increase of arachidonic acid, which is subsequently metabolized into eicosanoids (including leukotrienes [LT] and prostaglandins [PG]).

It has been shown that dysmenorrheic women receiving no medication had four times higher endometrial PGF2-α levels than the eumenorrheic women on the first day of the menstrual period [26]. The level of PGF2-α was directly proportional to the intensity of menstrual pain and symptoms of dysmenorrhea [4]. Moreover, primary dysmenorrhea is associated with higher concentrations of menstrual LT-C4/D4 [27]. Since LT-C4 has binding sites in myometrial cells [28], it is possible that LT contribute to uterine hypercontractility.

Indeed, primary dysmenorrhea patients have higher basal uterine tone, active pressures, and increased number of uterine contractions compared to normal women [4]. Thus, the cascade response of PG and LT, which mediate hyperalgesia and inflammatory responses, may cause vasoconstriction, ischemia and myometrial contraction [3].

In addition to peripheral mechanisms, sensitization in the central nervous system may also play a role in dysmenorrhea. Using electric stimulation, it has been demonstrated that hyperalgesia exist in deep tissue (i.e., subcutaneous and muscle) at both referred and non-referred pain sites throughout the menstrual cycle in dysmenorrhea patients [29].

Furthermore, during the menstrual period hyperalgesia extends to the skin as tested with thermal and pressure stimulation but not tactile stimulation [30].

In a laser-evoked potential study, dysmenorrheic patients revealed longer latencies of pain-evoked potentials and a higher magnitude of supra-threshold
pain stimulation compared to healthy subjects [24]. The aforementioned studies indicate an enhanced pain perception in patients with dysmenorrhea, possibly as a result of both peripheral and central sensitization.

1.5. Chronification of Pain

Prolonged nociceptive input from the periphery to the central nervous system can induce functional and structural alterations throughout the nervous system and is known to result in central sensitization [31].

Initially, peripheral and central sensitization act together to induce spontaneous ongoing pain, enhanced pain sensitivity (hyperalgesia), a lowered pain threshold turning non-nociceptive input into pain (allodynia), and referred pain. With further pain chronification, pathological changes at peripheral, spinal and supraspinal levels take place. Some of these changes may become independent of the peripheral input and even persist in their absence.

At the supraspinal level, brain imaging studies have shown that chronic pain may induce changes in brain chemistry [32, 33], brain processing [34-37], and in macroscopic brain structures [38].

Clinical pain states of heterogeneous etiology have been associated with abnormal cognitive/ emotional and sensory processing albeit with subtle differences between clinical states [34]. Because chronic pain is a heterogeneous group of conditions arising from various tissue systems, the different types cannot be expected to result in identical brain alterations. Factors such as cyclicity, pain history, pain distribution, cause of pain, and psychological setup varies across individuals as well as studies. Chronic pain is discomforting and distressing for most individuals and is highly comorbid with mood and anxiety disorders [39]. Psychiatric comorbidity may further result in separate central changes and in a specific brain "signature".

Section II. Structural and Functional Alterations in the Brain of Dysmenorrhea Patients

In the past two decades, non-invasive functional brain imaging techniques have greatly increased our knowledge of pain processing in the brain. It is now well-accepted that noxious information is processed by a widely distributed,
hierarchically-interconnected neural network, commonly referred to as the “pain matrix”, in the brain [40, 41]. The majority of functional brain imaging studies, mainly conducted using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), examined the brain processing in response to painful cutaneous stimulation.

The most commonly found brain regions responding to cutaneous pain stimuli include primary somatosensory cortex (SI), secondary somatosensory cortex (SII), anterior cingulate cortex (ACC), insula, and thalamus. Other less consistently engaged regions include the prefrontal cortex (PFC), premotor and motor cortex, and cerebellum [34, 37, 42].

Other regions such as the basal ganglia, amygdala, hippocampus, and parietal and temporal cortices may also be engaged depending on the particular pain condition or comparison [37]. The neuroanatomical regions involved in pain processing have simplistically been categorized as belonging to the sensory-discriminatory related “lateral pain system” and/or the affective-cognitive related “medial pain system” [43].

An additional component of pain processing may involve a motor component such as in, e.g., motor-defensive or reorienting responses. Evidences suggests that the SI, SII, and posterior insula are associated with the sensory-discriminative aspects of pain processing while ACC, anterior insula and PFC are associated with affective-cognitive aspects of pain processing [34, 44-46].

However, because the role of different brain regions are more or less dependednt upon the interplay of factors influencing pain perception, the categorization is not always consistent regarding the function of particular regions, especially when concerned with higher-order pain processing areas. It is important to emphasize that although acute cutaneous pain shares many commonalities in brain processing with acute muscle pain [47], substantial differences exist when compared to acute visceral pain.

2.1. Visceral Pain Processing in the Brain

The cumulating literature on brain processing of visceral pain has revealed overlapping but also distinct brain networks processing visceral and cutaneous pain. The different brain activation patterns between the two types of pain may partially be attributed to the separate afferent pathways.

Cutaneous nociceptive input are transmitted to the brain via the lateral spinothalamic tract (STT) while nociceptive input from visceral organs are
transmitted not only via the lateral STT but also via multiple other pathways including the vagal, glossopharyngeal, and cranial nerves and the spinal dorsal column (DC) [48-51].

An early meta-analysis of visceral brain imaging studies revealed that the most consistently activated regions were the anterior insula and ACC [35]. The PFC, orbitofrontal cortex (OFC), motor cortex, SI, SII, thalamus, and inferior parietal cortex were less commonly reported. The least consistently reported regions were the subcortical regions such as amygdala, periaqueductal gray matter (PAG), lentiform nucleus, and caudate nucleus [35, 48, 52].

These activation patterns may partially explain the clinical observations that somatic sensation is well localized while localization of visceral sensation is dull and poorly localized [48]. It is noteworthy to mention that the activation maps of visceral pain are inconsistent across different visceral disease entities and stimulation sites.

Apparently, different parts of the gastrointestinal tract may preferentially engage different brain regions. Visceral stimulation using rectal distension in both healthy subjects and in patients with irritable bowel syndrome (IBS) results in a more pronounced activation in the medial pain system (i.e., PFC, OFC, and rostral ACC) and less in the lateral pain system (i.e., SI and SII) [35, 53-56]. In contrast, esophageal stimulation more frequently engage sensorimotor regions, including SI and SII, and dorsal ACC [52, 57-60].

Recent studies using painful proximal gastric distension in both healthy subjects and in functional dyspepsia patients reported significant activation in SI/SII areas [61-63], while earlier studies in healthy subjects stimulating the gastric fundus and antrum failed to engage SI/SII [48, 64].

Thus, it is likely that visceral pain originating from different organs may result in different activation patterns of the brain. Some of the important regions and pathways found to be involved in visceral pain processing are illustrated in Figure 1A.

### 2.2. Structural Brain Alterations in Dysmenorrhea

#### 2.2.1. Gray Matter Alterations in Chronic Pain

Structural alterations in the grey matter (GM) of the brain can be studied by segmentation of high-resolution anatomical MRI scans. Convergent studies have demonstrated that chronic sustained pain of various etiologies is accompanied by GM alterations in the brain.
Functional and Structural Brain Alterations ...

Figure 1. Diagram of the normal and dysregulated visceral pain pathways. (A) In women without dysmenorrhea, the visceral pain networks are regulated by the dorsolateral prefrontal cortex (dIPFC). The visceral pain network includes the spinal dorsal column (DC), midbrain, thalamus, lateral orbitofrontal cortex (lOFC)/anterior insula (ant insula), medial orbitofrontal cortex (mOFC), medial prefrontal cortex (mPFC), and hypothalamus. Hypothalamus is the initial point of the hypothalamic-pituitary-adrenal (HPA) and hypothalamic-pituitary-gonadal (HPG) axis. (B) After long-term suffering from dysmenorrhea, changes in dIPFC may result in a dysregulated visceral pain network. "(-)" denotes inhibitory input. Bold line and dashed line denote enhanced and dysfunctional pathways, respectively.
It has been reported that headache and migraine have been associated with GM atrophy mainly in affective related regions (e.g. ACC, posterior cingulate cortex [PCC], insula, OFC, and parahippocampal gyrus) [65-67], while chronic back pain mainly has been associated with changes in sensorimotor regions (e.g. PFC, SI, and thalamus) [68, 69].

In patients with IBS, cortical thinning has been found in ACC and anterior insula and decreased GM density was found in thalamus [70, 71]. Although the functional significance of these changes remains to be resolved, structural brain alterations have been suggested to be the consequence of ongoing nociceptive stimulation, causative to the disease pathogenesis, and/or an integral part of the chronification process [72].

This has led to the notion that maladaptive brain atrophy that may be responsible for development and maintenance of the pain state. In context of chronic pain, maladaptive plasticity in response to protracted nociceptive input may result in decreased inhibition or increased facilitation.

On the contrary, acute nociceptive infliction in healthy individuals has been associated with adaptive plasticity, manifested as regional hypertrophy in pain-related areas [73].

Adaptive plasticity may serve as a protective mechanism against ongoing input in order to maintain homeostasis. Thus, due to its cyclical nature of pain and pain-free states, it is highly possible that menstrual pain is associated with both state- and trait-related structural abnormalities in the brain. Where state-related changes are associated with the presence of menstrual pain, trait-related changes exist even in the absence of symptoms.

2.2.2. White Matter Alterations in Chronic Pain

The integrity of white matter (WM) tracts can be studied using diffusion tensor imaging (DTI). The DTI measures the diffusion of water in different directions and provides information about the microstructure of WM tracts.

The fractional anisotropy (FA), which calculated from DTI, can be used as an index to further quantify the directional level of WM tracts.

Abnormal FA values have been found in pain-related brain regions and pathways in various chronic pain conditions. In fibromyalgia patients, the thalamus, insula, and thalamocortical tracts revealed decreased FA values while SI, PFC, amygdala, and hippocampus revealed increase FA values compared to normal controls [74]. The neuropathic pain patients also revealed WM changes in OFC, PFC, and posterior parietal cortex regions [75].

Moreover, the patient with IBS revealed increase FA values near insula. The clinical characteristics of IBS (e.g. pain severity, pain unpleasantness, and
IBS duration) further correlated with the FA values near different subregions of insula [76]. Thus, like the GM alterations in brain in chronic pain, the WM in the brain may also be altered after long-term pain suffering.

2.2.3. State- and Trait-Related Grey Matter Alterations in Dysmenorrhea

In our studies [20 and unpublished observation], we addressed possible rapid state-related and long-term trait-related structural alterations of the brain in dysmenorrhea. During the pain-free state, dysmenorrhea patients disclosed trait-related atrophic GM changes in regions involved in pain transmission, higher level sensory processing, and affect regulation, namely medial PFC (mPFC), right central and ventral portions of precuneus, bilateral SII/posterior insula, right superior temporal gyrus (STG)/mid insula, right culmen, and left cerebellar tonsil. Trait-related hypertrophic GM alterations were found in regions involved in pain modulation and in regulation of the endocrine function, namely right posterior hippocampus/parahippocampus, ACC/dorsal PCC (dPCC), dorsal midbrain (PAG), hypothalamus, left ventral portion of precuneus, left STG/middle temporal gyrus (MTG), and right cerebellar tonsil. Moreover, trait-related GM changes in key regions involved in top-down pain modulation and in generation of negative affect were related to clinical symptoms.

The right mPFC, bilateral dorsolateral PFC (dPFC), right premotor cortex, and right lateral OFC (IOFC)/anterior insula were negatively while the right ACC/dPCC and bilateral medial OFC (mOFC) were positively correlated with the menstrual pain experience (i.e., total scores of pain rating index in the McGill Pain Questionnaire [MPQ]). Considering the early onset of dysmenorrhea, these results suggest vulnerability of the adolescent brain to long-term menstrual pain suffering.

Several of the regions exhibiting trait-related alterations also exhibited state-related changes (i.e., between pain and pain-free state) in dysmenorrhea patients (Figure 2). Greater state-related hypertrophic changes were observed in mOFC, right central portion of precuneus, and right hypothalamus while greater atrophic changes were found in SII and ACC/dPCC in dysmenorrhea than control. Moreover, in dysmenorrhea subjects the GM volume differences within hypothalamus and thalamus were significantly positively and negatively correlated with the current menstrual pain experience scores, respectively. These findings suggest that spontaneous recurrent pain results in rapid state-related changes in macroscopic brain structures, and that adaptive and mal-adaptive changes may be engaged simultaneously and dynamically.
Figure 2. State- and trait-related brain gray matter volume changes in dysmenorrhea patients. Both (A) state-related (during menstrual pain period) and (B) trait-related (during pain-free period) gray matter volume analysis revealed hypertrophic and atrophic changes in hypothalamus and secondary somatosensory area (SII), respectively. The regions are threshold with uncorrected voxel $p<0.005$ and a cluster extension larger than 150 voxels. The warm colors represent increased volume while cold colors represent decreased volume.

2.2.4. State-and Trait-Related White Matter Alterations in Dysmenorrhea

Long-term suffering from dysmenorrhea may not only alter regional GM volumes but also the local WM tracts in the brain. Using FA as an index, dysmenorrhea patients exhibited trait-related WM tract alterations in pain transmission and modulation pathways. Decreased FA values were found in the corticospinal tract near SI and in the anterior thalamic radiations near the superior frontal gyrus. The corticospinal tract is a descending projection from the cortex to the spinal cord [77], which is functionally associated with the control of sensory afferent input and supports the voluntary execution of skilled movements [78]. The WM alterations in the corticospinal tract may therefore represent an abnormal structural change in the sensory feed-forward loop to the spinal dorsal horn that potentially could contribute in part to the central sensitization known to exist in dysmenorrhea [29, 30]. The anterior thalamic radiation reciprocally connects the anterior and medial regions of the thalamus with the prefrontal cortex [79]. The prefrontal cortex is considered a
key region in pain modulation and emotional regulation and the anterior thalamic region further connects with regions functionally related to the affective dimension of pain [80, 81]. Thus, the FA decrease near the frontal region along the anterior thalamic radiation may reflect a structural change associated with the dysregulation of the affective component of the menstrual pain experience. State-related changes in WM tracts were not found in dysmenorrhea patients suggesting the structural WM connectivity to be less influenced by acute pain than regional GM volumes. Overall, these findings should be appreciated in light of the aforementioned abnormal GM changes in the brain, and suggest a substantial impact of menstrual pain on the brain of dysmenorrhea patients.

2.3. Functional Brain Alterations in Dysmenorrhea

Clinical pain of heterogeneous etiology have been associated with enhanced cognitive/ emotional processing and decreased sensory processing albeit with subtle differences between clinical states [34]. A meta-analysis study including 68 experimental pain studies in normal subjects and 30 clinical pain studies revealed that chronic clinical pain conditions more frequently activated PFC (clinical conditions: 81%, normal subjects: 55%) while experimental pain in normal subjects more frequently activated SI (clinical conditions: 28%, normal subjects: 75%), SII (clinical conditions: 20%, normal subjects: 75%), insula (clinical conditions: 58%, normal subjects: 94%), and ACC (clinical conditions: 45%, normal subjects: 87%) [34]. More specific to visceral pain, ACC activity in normal subjects was found to be correlated with pain intensity levels of rectal distension but this was not the case for IBS patients [54]. Compared to patients with ulcerative colitis and control subjects, IBS patients have increased activity in response to rectal distention within the amygdala, PFC, and other limbic/ paralimbic regions [53]. Another study on osteoarthritic knee pain demonstrated that spontaneous arthritic pain was associated with increased activity in the cingulate cortex, thalamus, and the amygdala when compared to experimental knee pain [82]. Similarly, involvement of the medial prefrontal cortex (mPFC), including the rostral ACC, during episodes of high sustained ongoing chronic back pain has been reported, and the activity of mPFC was found to be strongly related to the intensity of chronic back pain [83]. Thus, chronic pain patients may have overlapping and distinct brain activation patterns to pain compared with normal subjects.
In order to address the possible state-related changes in brain metabolism associated with menstrual pain, we conducted an $^{18}$fluoro-deoxyglucose PET study in dysmenorrhea patients and in healthy controls [25]. When comparing the pain state with the pain-free state in dysmenorrhea patients, increased regional glucose metabolism was found in the pulvinar of thalamus, IOFC, mOFC, and mPFC.

These regions are known to be involved in pain transmission, monitoring/generation of the subjective affective experience, and transferring of visceral information to visceromotor output areas. For the same comparison, decreased regional metabolism was found in lateral somatic sensorimotor areas and included dIPFC, SII, posterior insula, and STG/MTG. Such differences were not found in healthy controls.

For dysmenorrhea patients in the pain state, the metabolism of IOFC and mOFC were further positively correlated with the menstrual pain experience while SII, posterior insula, and STG/MTG were negatively correlated with the menstrual pain experience. Since dysfunctional dIPFC mechanisms may lead to disinhibition of orbitofrontal networks resulting in increased negative affect [69], it is possible that reduced dIPFC metabolism and increased metabolism in thalamus and orbitofrontal regions may represent disinhibition from the dIPFC to the thalamic and orbitofrontal circuits. Such a mechanism may be a key factor in the generation of pain and hyperalgesia in dysmenorrhea patients by maintaining spinal and thalamic sensitization while increasing negative affects.

**Section III. Possible Impact of Brain Alterations in Response to Menstrual Pain**

Our line of studies showed that menstrual pain is not only accompanied by abnormal cerebral metabolism but also structural WM and GM changes in brain regions involved in various aspects of pain processing (Figure 1B and Figure 2).

Overall these aspects included top-down pain modulation, affective regulation, and pain transmission. Functional and structural alterations may either influence, or be influenced by, the long-term cyclic suffering from menstrual pain.
3.1. Central Sensitization

Previous studies indicate that central sensitization exists in patients with dysmenorrhea [24, 29, 30]. One plausible contributing mechanism may involve disinhibition of key brain circuits by dIPFC, a region involved in top-down pain modulation [84] (Figure 1B). In dysmenorrhea patients, we observed hypo-metabolism in dIPFC during menstrual pain and a negative correlation between GM volumes in dIPFC and the menstrual pain experience [20, 25]. Together, these findings point to a dysfunctional dIPFC that is further negatively influenced by pain severity. A dysfunctional dIPFC has previously been implicated in disinhibition of orbitofrontal networks, including mPFC and ACC, which may lead to enhanced negative affect [69, 84]. Congruent with this, we also found hyper-metabolism during menstrual pain in mOFC and a positive correlation between GM volumes in mOFC and the menstrual pain experience, while atrophic trait-related GM changes were found in mPFC, which negatively correlated with the menstrual pain experience [20, 25].

A dysfunctional dIPFC may also implicate a dis-inhibited visceral afferent pathway. The dIPFC may influence pain transmission between the midbrain and thalamus and at the level of the anterior insula resulting in the modulation of pain intensity and affect, respectively [84](Figure 1B). In animals, visceral nociceptive afferents are known to project to the ventral-posterior portion of the thalamus via the DC pathway in the spinal cord [51, 85, 86], and then project to the visceral sensory areas in the lateral posterior OFC/ anterior insula [87, 88] (Figure 1B). The DC pathway is considered part of a facilitatory loop that can intensify noxious visceral responses and may be necessary for the maintenance of sensitization associated with chronic visceral pain [89, 90]. The pulvinar, a nucleus located in the posterior portion of the thalamus, has been implicated in a relay of somatosensory information and in directed attention towards sensory stimuli [91]. Furthermore, the IOFC of the right hemisphere has preponderantly been associated with evaluation of aversive stimuli and regulation of negative emotion [92]. Hence, our results suggest a disinhibition of a thalamo-orbitofrontal-prefrontal network that may promote central sensitization in dysmenorrhea in both functional and structural aspects.

Other possible mechanisms that may contribute to maintaining central sensitization involves the hypothalamus. The hypothalamus has the potential to influence menstrual pain through interacting pathways in which it has a decisive role (Figure 1B). The hypothalamus is part of a feedback loop in the hypothalamic-pituitary-gonadal axis which regulates the menstrual cycle. In
this loop, the hypothalamus responds to elevated estrogen levels and regulates uterine PG synthesis [93]. An abnormally elevated estrogen level has been found in the late luteal phase in women with primary dysmenorrhea [94], and higher endometrial PGF2-α levels have been found in dysmenorrheic women than in eumenorrheic women on the first day of the menstrual period [26]. Moreover, the level of PGF2-α was directly proportional to the menstrual pain intensity and symptoms of dysmenorrhea [4]. Thus, a periodic increased estrogen assault on the hypothalamus may take place which could result in longer-lasting reactive structural GM changes.

Hypothalamus is also a key component of the spino-bulbo-spinal loop, a pain modulatory pathway that may lead to enhanced negative affect and pain amplification [95 76](Figure 1B). Another key region in this loop is the PAG which is well-known for its role in pain modulation. Both of these regions revealed trait-related structural alterations in our study [20]. Other regions providing cortical feedback to this loop include hippocampus and ACC. These two regions also exhibited trait-related hypertrophic changes [20]. The ACC/dPCC is a region consistently associated with pain responses in chronic pain patients [45] and alterations in the hippocampus and amygdala have been reported in animal models of chronic neuropathic pain [96]. In conjunction with the aforementioned dis-inhibited thalamo-orbitofrontal-prefrontal network, the spino-bulbo-spinal loop may play a down-stream role to the central sensitization phenomena since anatomically hypothalamus and PAG receives afferent projections from the mPFC and mOFC [97]. These medial structures could reflect mal-adaptive plasticity underpinning the hyperalgesia known to exist in dysmenorrhea patients.

3.2. Adolescent Health, Pre-Disposition and Comorbidities

Considering that the dysmenorrhea populations in our studies were relatively young and had suffered from regular menstrual pain since adolescence, brain maturation most likely was in progress concomitant with the onset of dysmenorrhea. Since brain maturation is ongoing in adolescents and is more stable in adults [98, 99], our results may not only indicate that the adolescent brain is vulnerable to reoccurring menstrual pain but also that this vulnerability affects the brain at a later stage in adulthood.

Emotional and physiological stress are integral components of dysmenorrhea and two key factors profoundly influencing the brain. Dysmenorrhea has been associated with increased perceived stress levels and
the menstrual pain is thought to be aggravated by emotional stress [100]. The hypothalamus, which we found to be enlarged in dysmenorrhea, is also involved in shaping of the physiological stress response through the hypothalamic-pituitary-adrenal (HPA) axis (Figure 1B). Cortisol, a stress indicator secreted from the adrenal cortex into circulation, has been found to vary across the menstrual cycle in women with dysmenorrhea with the highest level during the menstrual phase [101]. Another study found a decreased level of cortisol in dysmenorrhea when collapsing data across the menstrual cycle and a negative correlation of mean cortisol with the duration of dysmenorrhea [102]. However, these findings possibly represent stimulated cortisol and indicate increasingly abnormal stress regulation in face of stimulated stress. One plausible mechanism of HPA dysregulation involves abnormal hippocampal feedback to the hypothalamus since ongoing stress impairs the negative feedback mechanism from the hippocampus to the HPA axis [103]. Congruent with this, trait-related hippocampal hypertrophy was found in our study [20].

The adolescent brain is functionally and structurally sensitive to stress as evidenced by the literature concerned with early-life trauma [104-106]. The sensitivity most likely depends on several factors including stress type, duration, and age of onset. In animal models using adolescent rodents (e.g., 30 to 60 days), chronic stress altered corticolimbic structures, e.g. the hippocampus, amygdala, and prefrontal cortex [107], involved in the modulation of the HPA axis. Furthermore, the recovery period of dendritic morphological changes in prefrontal regions after chronic stress is longer in adolescents than in adulthood [108, 109]. It is therefore possible that repeated stress may have a cumulative effect on stress-induced structural plasticity [110]. Thus, cyclic recurrent menstrual pain has the potential to greatly influence brain development in adolescence.

Taking the above into account, it is possible that menstrual pain may act as a pre-disposing factor for other clinical conditions. It has previously been proposed that dysmenorrhea may act as a precursor stage in women who progress to chronic pelvic pain, since dysmenorrhea often is reported prior to the development of chronic pelvic pain [111]. Premenstrual dysphoric disorder has also been associated with dysmenorrhea and the occurrence of premenstrual dysphoric disorder significantly correlated with the severity of menstrual pain [23, 112]. Other pain conditions that are more prevalent in females [18, 19] and are often comorbid with dysmenorrhea [20] include IBS and fibromyalgia. Indications of enhanced stress responsiveness and a dysregulated HPA axis exist in IBS patients [113, 114]. Interestingly, like in
our studies, the hypothalamus was also found to be enlarged in IBS patients [70]. Also, abnormal hippocampal glutamatergic neurotransmission has been found in IBS patients suggesting altered HPA feedback [33]. Taken together, it is conceivable that the early onset of dysmenorrhea may result in a mal-adaptive effect that predisposes to other clinical conditions. Repeated state-related brain alterations induced by menstrual pain in adolescence may result in a cumulative effect that contributes to the aforementioned pre-disposition effect and to the chronification of other clinical pain conditions.

Conclusion

Dysmenorrhea is a widely presented gynecological disorder for women in the childbearing age. It is often comorbid with other idiopathic pain conditions. In a series of studies, we demonstrated that trait- and state-related brain alterations, both functionally and structurally, exist in dysmenorrhea. Overall these alterations included regions involved in top-down pain modulation, affective regulation, and pain transmission. Our studies suggest that adaptive and mal-adaptive changes in the brain may be engaged simultaneously and dynamically in dysmenorrhea. These changes may further provide a possible mechanism for cyclic recurrent menstrual pain to pre-dispose or contribute to the chronification of other clinical pain conditions. Like the migraine, primary dysmenorrhea should be considered a chronic disease with episodic features but largely confined to the menstrual phase. A serious revisit of primary dysmenorrhea regarding its impact on the brain and long-term clinical consequences is needed.

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