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Altered brain connectivity in dysmenorrhea: pain modulation and the motor cortex

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Primary dysmenorrhea, menstrual pain without an identified cause, is a common and often debilitating problem. 15–20% of women fail to respond to conservative treatment, and experience significant reduction in quality of life [5]. An important consideration, that we and others have proposed, is that these treatment failures may reflect a completely different phenotype, where the primary disorder is aberrant central processing of pain rather than solely peripherally based uterine inflammation [4]. Consistent with this idea, high rates of comorbidity have been identified between dysmenorrhea and other idiopathic pain disorders, notably irritable bowel syndrome and painful bladder syndrome [18]. The epidemiological overlap with these visceral pain conditions suggests sensitization in the central nervous system may also play a role in menstrual uterine pain. Correspondingly, there is a growing body of evidence showing that some dysmenorrhea sufferers exhibit widespread reductions in both somatic [2; 6] and visceral [16] hyperalgesia, suggesting fundamental changes in central pain modulatory systems.

In this issue, Wei and colleagues tested the hypothesis that brain networks, known to modulate pain, might display markers of dysfunction in women with primary dysmenorrhea [17]. They performed resting state functional magnetic resonance imaging (fMRI) of the brain in women both with and without primary dysmenorrhea at two time points: during the menstrual phase and during the periovulatory phase. Resting state fMRI is an established approach to estimate strength of interaction (functional connectivity) among brain regions. As in previous studies, by examining women at these two time points, the authors were able to disambiguate functional connectivity changes related to the active experience of pain during the menstrual phase from functional connectivity changes more intrinsic to the individual during the periovulatory phase. Due to the wealth of literature showing a role for periaqueductal gray (PAG) in descending pain modulation, the authors hypothesized the

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functional connectivity of PAG might distinguish women with and without primary dysmenorrhea. During the menstrual phase, women with primary dysmenorrhea had increased functional connectivity, compared to healthy controls, between the PAG and medial sensorimotor areas near the midline of the brain (stronger changes are reported in motor compared to sensory areas). However, during the periovulatory phase, women with primary dysmenorrhea had decreased functional connectivity with the "default mode network", a group of brain regions known to be important in healthy brain function.

A particularly exciting feature of the report of Wei and colleagues is potentially convergent brain imaging findings across chronic visceral pain disorders. Recent studies have reported functional connectivity disturbances in medial brain motor areas in women with interstitial cystitis/painful bladder syndrome [9], in men with chronic prostatitis/chronic pelvic pain syndrome [10], and also in women with localized provoked vulvodynia [7]. Recent anatomical connectivity studies in rats using the retrograde transneuronal labelling studies suggest that visceral structures may be more strongly represented in medial brain motor areas than any other cortical area; also, the visceral representation in motor cortex is aligned with the more medial somatic motor representation of trunk and lower limb muscles [12]. In humans, muscles such as the pelvic floor [1], abdominals [15], and toes [14] are represented in more medial areas of motor cortex, and dysfunction of these regions has been suggested in chronic pain [8]. These data collectively suggest that medial brain motor areas may have important, but underrecognized modulatory influence on both somatic and visceral processes.

The specific relationship between PAG and the motor cortex in dysmenorrhea is also supported by recent reviews of therapeutic transcranial magnetic stimulation (TMS). Motor cortex is the only brain region for which strong evidence exists for the analgesic effects of TMS, possibly through the indirect (multi-synaptic) interaction of motor cortex with the PAG [11]. The findings of Wei and colleagues in this issue might suggest that the pain of primary dysmenorrhea during the menstrual phase could relate to a dysfunctional pain modulatory system involving the motor cortex and PAG. If the importance of connections between motor cortex and the viscera shown in animal models can be repeatably demonstrated in humans, it is possible that motor cortical dysfunction in visceral pain conditions could result in a wide array of effects on somatic-motor activity, visceral-motor activity, and descending pain modulation.

The study of Wei and colleagues in this issue opens interesting questions. It remains unclear if the PAG functional connectivity changes during the menstrual phase are more or less important in mediating symptoms compared to the changes during the periovulatory phase. Functional connectivity changes within the default mode network during the periovulatory phase are intriguing given the extensive previous literature on the default mode network in chronic pain [3; 13] and that these changes exist even when an individual is not experiencing the active pain of the menstrual phase (i.e. may represent a trait of the individual). It is possible that PAG functional connectivity changes to the default mode network may be an ongoing representation of cumulative pain experienced during the menstrual phase, pain which is actually generated by functional connectivity dysfunction between medial brain motor regions and the PAG. Future longitudinal studies with repeated neuroimaging during

both the menstrual and periovulatory phases, and associated symptoms, will be necessary to tease out the relative importance of PAG functional connectivity to the default mode network compared to medial brain motor areas. The work of Wei and colleagues is nonetheless very important to stimulate future research in motor cortical involvement in pain processes.

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