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Original Reports

Functional Connectivity Is Associated With Altered Brain Chemistry in Women With Endometriosis-Associated Chronic Pelvic Pain

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Abstract: **In contrast to women with relatively asymptomatic endometriosis, women with endometriosis-associated chronic pelvic pain (CPP) exhibit nonpelvic hyperalgesia and decreased gray matter volume in key neural pain processing regions. Although these findings suggest central pain amplification in endometriosis-associated CPP, the underlying changes in brain chemistry and function associated with central pain amplification remain unknown. We performed proton spectroscopy and seed-based resting functional connectivity magnetic resonance imaging to determine whether women with endometriosis display differences in insula excitatory neurotransmitter concentrations or intrinsic brain connectivity to other pain-related brain regions. Relative to age-matched pain-free controls, women with endometriosis-associated CPP displayed increased levels of combined glutamine-glutamate (Glx) within the anterior insula and greater anterior insula connectivity to the medial prefrontal cortex (mPFC). Increased connectivity between these regions was positively correlated with anterior insula Glx concentrations (r = .87), as well as clinical anxiety (r = .61, *P* = .02), depression (r = .60, *P* = .03), and pain intensity (r = .55, *P* = .05). There were no significant differences in insula metabolite levels or resting-state connectivity in endometriosis patients without CPP versus controls. We conclude that enhanced anterior insula glutamatergic neurotransmission and connectivity with the mPFC, key regions of the salience and default mode networks, may play a role in the pathophysiology of CPP independent of the presence of endometriosis.**

***Perspective:** Similar to other chronic pain conditions, endometriosis-associated pelvic pain is associated with altered brain chemistry and function in pain processing regions. These findings support central pain amplification as a mechanism of chronic pelvic pain, and clinicians should consider the use of adjunctive therapies that target central pain dysfunction in these women.*

Key words: *Endometriosis, chronic pelvic pain, neuroimaging, glutamate, functional connectivity.*

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Endometriosis is a common gynecologic condition estimated to affect 10 to 15% of reproductive-aged women and up to 80% of women with chronic pelvic pain (CPP).[21,43,45,62,68] Endometriosis is defined as the presence of endometrial glands and stroma (referred to as endometriosis implants) outside the uterus. Thus, it is a histologic diagnosis that requires surgical evaluation and biopsy. Although endometriosis is the most common finding among women undergoing surgery for CPP and likely contributes to pain in at least some of these women, it is unclear whether endometriosis is the underlying cause of pelvic pain in all of these women. Little is known about the mechanisms involved in the development of chronic pain in this population. As with most chronic pain syndromes, the presence and severity of organic disease do not correlate with symptom severity and many women with endometriosis, even severe, experience little if any pain.[7,38,54,67] Furthermore, standard therapies targeting endometriosis implants are not consistently effective and pain frequently recurs, often without evidence of residual pelvic disease.[57,61,66] Against this background, endometriosis must be viewed as an important but insufficient factor in the development of CPP.

Central nervous system (CNS) abnormalities in pain processing have been identified in multiple chronic pain syndromes, which often occur in the absence of identifiable disease in the area of pain. Findings include hyperalgesia within and outside areas of clinical pain, parallel increases in neural activity, as well as structural alterations in pain-related cortical areas.[16,28,31,47,56] More recently, aberrant brain neurochemistry and functional connectivity have also been identified in patients with other chronic pain conditions. The insula, a brain region involved in the integration of interoceptive, affective, and cognitive signals, is a primary focus in pain neuroimaging studies because it is one of the most consistently activated regions during acute and chronic pain.[3] For example, increased levels of excitatory neurotransmitters within the posterior insula and decreased levels of inhibitory neurotransmitters within the anterior insula have been identified in patients with fibromyalgia.[25,33] Furthermore, resting-state brain connectivity of the insula is augmented in neural pain processing regions of patients with fibromyalgia relative to pain-free controls.[39,52] These neural signals likely play a role in the underlying pathophysiology of chronic pain and may also be useful in clinical medicine because they are correlated with important patient-centered outcomes, such as clinical pain intensity and response to pharmacotherapy used to treat chronic pain.[32,51]

Our group has previously demonstrated that women with CPP, both with and without endometriosis, also exhibit hyperalgesia in a nonpelvic site as well as decreases in regional gray matter volume (GMV) in brain regions associated with pain processing, including the thalamus, cingulate gyrus, putamen, and insula, suggesting a similar problem of pain amplification related to CNS changes.[5,6] Although various neural mechanisms contributing to pain amplification have been identified in other pain syndromes, the precise nature of these neural changes remain unknown in women with endometriosis-associated pelvic pain. Identifying specific neural mechanisms associated with pain amplification is necessary to develop targeted treatment strategies for women who are not responsive to traditional medical and surgical therapies for endometriosis and other causes of CPP.

The primary objective of this study was to use proton magnetic resonance spectroscopy (^{1}H-MRS) and functional connectivity magnetic resonance imaging (MRI) techniques to determine whether women with endometriosis-associated CPP display changes in excitatory neurotransmitter concentrations in the insula or changes in intrinsic brain connectivity between the insula and other pain-related brain structures. To investigate whether such neuroimaging changes are related to endometriosis versus the presence of CPP, we also investigated women with similar pelvic disease (endometriosis) but without CPP. As previously demonstrated in other chronic pain conditions, we hypothesized that endometriosis-associated CPP is associated with increased levels of excitatory neurotransmitters in the insula and increased intrinsic brain connectivity of the insula to other brain regions associated with pain perception and modulation and that these findings would not be identified in patients with endometriosis without CPP.

Methods

Study Population and Case Definitions

The following subgroups of patient participants were included in this cross-sectional observational neuroimaging study: 17 women with endometriosis-associated CPP (⊕Endo⊕CPP) and 13 women with endometriosis without CPP (⊕Endo∅CPP). For exploratory purposes, an additional group of 6 women with CPP but no evidence of endometriosis (∅Endo⊕CPP) was also evaluated. Participants in this study were included in a previously published study of regional cerebral gray matter differences in women with CPP.[6] All participants were premenopausal women aged 18 to 52 years who had not undergone previous hysterectomy or bilateral oophorectomy. Women with endometriosis were recruited from a tertiary-care endometriosis and pelvic pain referral center, as well as through advertisement to the local community.

A pool of 24 pain-free healthy controls was recruited from ongoing studies using the same functional MRI (fMRI) protocol used in this study (mean age ± standard deviation [SD] = 29.3 ± 10.1 years). Controls were recruited through local advertisement. Because brain imaging parameters change with age and age varied significantly across patient subgroups, a subset of healthy controls was randomly chosen from a pool of 24 healthy controls to match the age distribution of the patient subgroups (14 controls were available for the ⊕Endo⊕CPP group and 12 controls were available