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Cortical and Psychological Mechanisms of Visceral Pain

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This thesis is dedicated to the numerous women suffering from dysmenorrhea daily and their struggle, as well as those who devote their lives to helping women suffering from chronic pain live happy and healthy lives.

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ABSTRACT

Objective: Dysmenorrhea is a type of visceral pain that affects numerous menstruating women and is defined by painful menstrual cramps and occurs in the absence of pelvic pathology. Cross-organ sensitization (COS), or the theory that uterine inflammation during menstruation generates neurogenic inflammation in other organs, may be a primary mechanism associated with pelvic pain in women with dysmenorrhea. Frontal activity during pain has been linked to attentional processing, with both dorsolateral prefrontal cortices (dlPFC) negatively correlated with intensity perception and unpleasantness. Since dysmenorrhea, depression, and somatization are associated with abnormalities in frontal cingulate networks, it is necessary to account for the potential effects on regional brain function that may be associated with co-occurring psychological symptoms in individuals experiencing dysmenorrhea. The results of the present study provide evidence that psychological symptoms and brain activity predict increased levels of visceral pain, specifically for women with dysmenorrhea and cross-organ sensitization (COS).

CHAPTER ONE

REVIEW OF THE RELEVANT LITERATURE

Overview of Visceral Pain: Dysmenorrhea and Cross-Organ Sensitization

Visceral pain is described as pain originating from the internal organs, most notable the thoracic, abdominal, and pelvic structures (Sikander & Dickenson, 2012). This type of pain is often diffuse and difficult to localize, making it challenging to treat. Among other types of visceral pain, one of the most debilitating endured by women across the world is dysmenorrhea. Dysmenorrhea is a gynecologic disorder that affects over 50% of menstruating women (Dawood, 1985). Dysmenorrhea is characterized by painful menstrual cramps and often occurs in the absence of pelvic pathology in young women (Dawood, 1985; Harel, 2006). Studies have shown that dysmenorrhea may be caused by excessive levels of inflammatory molecules, such as prostaglandin, within the uterus during menstruation (Dawood, 2006). Currently, nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit prostaglandin synthesis are commonly used to manage menstrual pain. Individuals who do not respond to NSAIDs can be prescribed estrogen/progestin oral contraceptive pills to on a cyclic or continuous regimen to reduce or suppress endometrial decidualization (French, 2005; Harel, 2006).

Dysmenorrhea is associated with a high amount of absenteeism from school and work, as well as related economic loss (Dawood, 1985). It is the leading cause of recurrent short-term school nonattendance in adolescent girls, with absentee issues often

continuing into adulthood (French, 2005). However, it is often poorly treated and disregarded by healthcare professionals, researchers, and even the very women experiencing it (Iacovides, Avidon, & Baker, 2015). Berkley (2013) found that despite its high prevalence, only 0.1% of published pain studies focused on dysmenorrhea, with only 3% of those studies published in pain journals. The majority of studies were published in women's health issues journals, which typically have a more limited readership and a lower impact factor. The amount of research studying dysmenorrhea is insufficient, particularly considering its high prevalence and extremely negative societal impact on girls and women.

Dysmenorrhea is currently accepted as a "normal" part of the menstrual cycle, but it has serious implications for pain sensitivity, mood, sleep, and overall quality of life. Women with primary dysmenorrhea have a significantly reduced quality of life, as well as a more negative mood, and disrupted sleep during menstruation compared with their own pain-free phases as well as the menstrual phase of pain-free women (Iacovides et al., 2015). Women with dysmenorrhea have reported higher sensitivity to experimental pain, even when they are not currently in phases of the menstrual cycle when pain is typically experienced (Iacovides et al., 2015). Susceptibility to pain sensitivity may be a primary risk factor for developing chronic pelvic pain for women with dysmenorrhea compared to women without dysmenorrhea. Notably, women without dysmenorrhea rarely develop chronic pelvic pain (Zondervan et al., 2001).

Cross-organ sensitization (COS), or the theory that uterine inflammation during menstruation can contribute to chronic pelvic pain by generating neurogenic

inflammation in other organs (Wesselmann, 2001) may be a primary mechanism associated with pelvic pain in women with dysmenorrhea. Dysmenorrhea sufferers with cross-organ sensitization (D+COS), compared to those without COS are theorized to experience higher rates of chronic visceral pain and are more susceptible to experimentally-induced pain, which are factors associated with poor quality of life outcomes (Westling et al., 2013). The implications of long-term pain sensitivity have been theorized to increase susceptibility to other chronic, visceral pain conditions, and these conditions are associated with higher rates of depression and other mood disorders (Haythornthwaite, Sieber, & Kerns, 1991).

The Neurobiological Effects and Oscillatory Activity of Visceral Pain

Although neural activity during menstrual pain is not yet well characterized, other forms of visceral pain including rectal pain evoke an increase in anterior cingulate cortex (ACC) activity with increasing levels in participants with chronic visceral pain (Mayer, Berman, Suyenobu, & Labus, 2005; Silverman et al., 1997). Conversely, lesioning (or inhibiting) ACC can eliminate the aversiveness to pain (Gu et al. 2010, Qu et al. 2011). ACC is a critical junction box for emotional processing, including pain perception during actual or stimulated pain delivery (Mayer, Berman, Suyenobu, & Labus, 2005; Silverman et al., 1997). Innovatively designed studies employing hypnotism have shown that ACC is primarily involved in the affective pain response, in contrast to other somatosensory areas are involved in raw detection of noxious input (Rainville et al. 1997).

The cingulate is part a set of network of frontal brain structures involved in top-down attentional control functions (Silton et al., 2010). Studies have shown that patients with visceral pain report more stress, anxiety, and anger before and after cued pain stimulation compared to healthy controls (Berman et al., 2008; Elsenbruch, Rosenberger, Elsenbruch et al., 2010). During the anticipation of a painful stimulus, patients are less likely to engage frontal mechanisms to down-regulate limbic activity. Activation of the frontal-limbic network has been theorized to support effective coping strategies during pain anticipation (Berman et al., 2008). This theory coincides well with the idea that an individual's perception of pain may be a primary determinant in the regulation of stress hormones (McCool, Smith, & Aberg, 2004). Additionally, hyperactivation of frontal cortices has been observed in patients with chronic pain. Frontal hyperactivity was shown to modulate cognitive appraisal of pain-relevant emotional signals from the limbic system (Bernstein & Frankenstein, 2002).

Frontal activity during pain has been linked to attentional processing, with both the right and left dorsolateral prefrontal cortices (dlPFC) negatively correlated with intensity perception and unpleasantness (Lorenz, Minoshima, & Casey, 2003; Lorenz & Casey, 2005). Lorenz and Casey (2005) showed that the inter-regional correlation of midbrain and medial thalamic activity was significantly reduced during high left dlPFC activity, which might suggest that pain affect may reduce connectivity within the midbrain-medial thalamic pathway. Right dlPFC was associated with a weakened relationship with the anterior insula in both intensity of pain and affect, suggesting that

the dlPFC actively regulates pain perception by modulating cortical pathways (Lorenz et al., 2003).

However, most visceral pain research has focused on gastrointestinal disorders, making it important to identify pain mechanisms in women with dysmenorrhea. Studies have shown that disinhibition of thalamo-orbitiofrontal-prefrontal networks may contribute to heightened pain sensitivity in individuals with primary dysmenorrhea by maintaining thalamic sensitization and increasing negative affect. (Tu, Niddam, Chao, Liu, & Hwang, 2009; Tu, Niddam, Chao, Chen, & Chen, 2010). This could induce compensatory inhibitory mechanisms in somatic sensorimotor regions, as well as dysfunctional dlPFC mechanisms, resulting in increased negative affect (Tu et al., 2009; Berkley, 2013). One of the only other studies on dysmenorrhea and pain (but not during menses), showed increased limbic activity in women with dysmenorrhea that was linked to duration and cortisol levels (Vincent 2011). It is quite possible that altered cortisol levels in depression/anxiety have lasting impact on the limbic system, the brain regions with highest density of neurons receptive to cortisol (Toda et al., 2006).

In order to characterize the time course of brain activity during clinical pain states, a number of electroencephalography (EEG) studies have been conducted, with an emphasis on measuring oscillatory activity. An inverse relationship with alpha power and reported pain scores has been observed, illustrating that a suppression of alpha oscillatory activity may be modulated by painful sensory input. Alpha activity could also be modulated by top-down regulations similar to mechanisms involving attention. Alpha activity is closely related to selective attention and is understood to actively gate the

incoming flow of information, enabling us to efficiently process our surroundings (Nir, Moont, Harari, & Yarnitsky, 2012; Gram, Graverson, Olesen, & Drewes, 2014; Peng, Hu, Zhang, & Hu, 2014; Peng, Babiloni, Mao, & Hu, 2015). Alpha generators are thought to exist in ACC, left insula, and bilateral dlPFC (Hunuke et al., 2013). Previous research has shown that the unique relationship between alpha power and the perception of tonic pain may indicate an individual's pain responsivity (Nir et al., 2012). Pre-stimulus alpha power is inversely related to perceived pain intensity, such that the dorsal ACC, medial prefrontal cortex, and left insula are related to increased pain (Hunuke et al., 2013). With potential implications for treatment of chronic pain, studies have shown that when the expectation of pain is reduced, alpha activity is dramatically increased (Babiloni et al., 2003; Hunuke et al., 2013). State-based measures of alpha activity indicate increased brain activity (decreased alpha) in response to anticipation and perception of pain.

Similarly, theta activity has also been shown to be implicated in visceral pain. Theta activity has been shown to be related to the experience of deep emotion, memory function, and the inhibition of elicited response. Similar to alpha activity, an inverse relationship with theta power and reported pain was seen in individuals experiencing chronic visceral pain compared to those without visceral pain (Drewes et al., 2008). This might suggest that theta activity may be modified in neuropathic visceral pain conditions (Drewes et al., 2008).

While research studying beta oscillatory activity is relatively sparse, recent evidence suggests that beta activity is related to attentional control processes. Beta

activity has been associated with the continuation of a cognitive set and the dominance of top-down influences that override the effect of potentially unexpected external events (Engel & Fries, 2010). Beta is theorized to increase during maintaining a cognitive set, particularly if a change or interruption is anticipated (Engel & Fries, 2010). Thus, enhanced beta activity is hypothesized to be associated with perseveration, or a reduction in cognitive control and flexibility (Engel & Fries, 2010). Individuals who live with chronic pain likely have poor cognitive control functions (Shackman et al., 2011), which could be related to frequent and perseverative rumination about pain or repetitively thinking about the causes and consequences of negative pain-related experiences (Sullivan, et al., 2001).

Indeed, beta power has been linked to neuropathic pain, such that beta power was localized to cortical networks involved in both cognitive control functions and pain response, such as anterior cingulate, prefrontal, and somatosensory cortices in patients with fibromyalgia (Stern et al., 2006). Gonzalez-Roldan et al., (2016) found that patients with fibromyalgia had enhanced beta activity during resting state, localized to right precentral gyrus, right middle frontal gyrus, superior frontal gyrus, midcingulate cortex, and right medial frontal gyrus. Related, our research has shown an increase in frontal beta activity in women with visceral pain while experiencing noxious stimuli (Hellman et al., under review). This study showed that women who reported visceral pain sensitivity also reported noxious sensory amplification compared to women who did not report pain sensitivity. The link between sensory amplification and visceral pain sensitivity was augmented by increased frontal beta oscillatory activity (Hellman et al., under review).

Enhanced beta power may be a risk factor or indicator of chronic pain. In the present study, it is hypothesized that a) women diagnosed with dysmenorrhea and cross organ sensitization (D+COS) will likely experience more enhanced frontal beta activity during resting state than women with dysmenorrhea but not COS, and b) we anticipate that resting state beta will be related to increased experimentally-induced visceral pain.

In the Montoya et al. (2016) study, anxiety and depression scores were negatively correlated with beta power such that enhanced resting state beta activity was associated with decreased cognitive control, but also less depressive symptoms in individuals with chronic pain. While at first blush this may appear counterintuitive since depression symptoms typically accompany attentional control deficits (Silton et al., 2011), these findings may be due to a premature assumption of the emergence of depressive symptoms since clinically significant depressive symptoms may not have yet emerged in the Montoya et al., (2016) sample. Longitudinal studies are need to better understand this relationship and to identify the risk factors for depression in women with chronic pain.

Co-Occurrence of Depression and Somatization in Dysmenorrhea

Dysmenorrhea has a high co-occurrence with depressive and anxiety disorders, which further contributes to debilitating outcomes (Latthe, 2006). In terms of general mood, studies have shown that women with dysmenorrhea have a more negative mood state during menstruation, and that both depression and anxiety are strongly associated with menstrual pain (Alonso & Coe, 2001; Dorn, Negriff, Huang, Pabst, & Hillman, 2009). Further, studies have shown that adolescent girls experiencing dysmenorrhea are at an increased risk for depression and anxiety, showing an early predisposition for mood

disorder with the potential for long-term adverse effects (Balık, Üstüner, Kağıtcı, & Şahin, 2014). Research investigating mood and anxiety disorders that co-occur with dysmenorrhea has been limited and additional research is necessary to better understand these comorbidities in order to inform and enhance intervention and treatment options. It remains unknown whether the neurobiological correlates of depression and anxiety symptoms predispose pain sensitivity and dysmenorrhea, and whether reducing menstrual pain affects depressive and anxiety symptoms.

Neurobiological Correlates of Depression.

In stark contrast to the dearth of information available on the brain mechanisms associated with dysmenorrhea, there is a wide body of literature focused on the brain mechanisms associated with depression. Lesion studies dated back as early as the 1970s (Gainotti, 1972) provided initial insight into the cerebral lateralization of positive and negative effect, with positive affect lateralized to the left prefrontal cortex (PFC) and negative affect lateralized to right PFC (Heller, 1990). Many studies have shown that depression is associated with a disturbance in lateralized prefrontal activity, with a dominant pattern of less left than right frontal activity emerging from the literature (Borod, 1992; Davidson, 1995; Davidson, 1998; Davidson & Irwin, 1999; Engels et al., 2007; Heller, Nitschke, Etienne, & Miller, 1997; Heller, Nitschke, & Miller, 1998; Henriques & Davidson, 1990, 1991; Herrington et al., 2005, 2010; Nitschke, Heller, Palmieri, & Miller, 1999; Tomarken, Davidson, Wheeler, & Doss, 1992). This asymmetrical pattern of alpha activity during resting state has been observed during episodes of current and remitted depression (Gotlib et al., 1998; Henriques and Davidson,

1990, 1991; Heller et al., 1997). Frontal alpha activity has been shown to predict future emotional response and negative affect, and it may be a candidate biomarker indicative of risk for depression (Allen & Reznik, 2015). Less is known about the role of depression and other oscillatory frequencies. Increased theta activity in frontal areas, particularly the ACC, has also been shown in depressed individuals (Rogers et al., 2004; Pizzagalli, 2011; Olbrich and Arns, 2013), and is thought to indicate responsivity to treatment (Pizzagalli et al., 2004). Even less is known about the role of beta in depression, but evidence suggests that patients with depression experience greater beta power, particularly noting differences in the right hemisphere (Knott et al., 2001; Olbrich & Arns, 2013)

Neurobiological Correlates of Somatization.

The relationship between somatization and visceral pain has been studied, particularly with regard to dysmenorrhea (Latthe, Mignini, & Gray, 2006; Bettendorf, Shay, & Tu, 2008). Somatization is often defined as a physical condition without an organic cause (Gureje, Simon, Ustun, & Goldberg, 1997). While some have argued that somatization is purely a cognitive and perceptual issue (Ursin, 1997, Erikson & Ursin, 2004) others researchers have started to investigate the biological factors that may play a role in the development and maintenance of somatization (Rief, 2005). Brain mechanisms that are believed to be implicated are known as the 'pain matrix', and include the spinal cord, brainstem, prefrontal and cingulate cortex, as well as somatosensory cortices (Jones et al, 2003). Specifically, prefrontal and parietal regions, implicated in attention and awareness, have been associated with somatic symptoms (Hakala et al., 2002). Further,

studies have shown that distraction from pain perception leads to reduced activity in pain centers in the brain, showing distinct biological factors contributing to both the invocation and relief from somatic symptoms.

Few studies have assessed the association among EEG oscillations and somatic symptoms in women with dysmenorrhea; However, disorders related to somatic distress, such as tinnitus, have been studied using EEG methods. In one study, increased alpha activity observed in the left insular region was correlated with higher levels of tinnitus symptoms, particularly shown in the left insular region (Van der Loo, 2011). Other studies utilizing bilateral transcranial direct current stimulation (tDCS) showed that tinnitus-related somatic complaints were decreased by modulating the anterior cingulate cortex (ACC) in resting-state brain activity (Vanneste, 2011). Source analysis showed a significant increase in alpha activity after tDCS in the ACC, when tDCS electrodes were placed over the dlPFC, (Vanneste, 2010; 2011). However, theta activity is not as well studied, yet its implications in visceral pain conditions is being discovered (Drewes et al., 2007; 2008; Graverson, 2012). Since somatic symptoms are correlated with visceral pain (Verne et al., 2001), and pain has been associated with theta (Drewes et al., 2007;2008), it is reasonable to surmise that theta may be associated with both somatization and pain; however, additional research is warranted to identify these relationships. Alpha, theta, and beta activity observed in frontal cortical regions likely affect sensory input as well as modulate emotional state. Although they are well characterized in depression and chronic pain, the importance of alpha, theta, and beta activity have not yet been examined in women with dysmenorrhea and D+COS who experience chronic visceral pain.

Examining the role of these specific oscillatory activities could provide key information into the brain factors associated with dysmenorrhea and D+COS, which could be increasing the experience of chronic visceral pain in these women.

<div align="center">**The Present Study**</div>

The preliminary research that has investigated the co-occurrence of psychological symptoms and menstrual disorders provides initial evidence that psychological and brain factors are associated with pain perception in women with dysmenorrhea and D+COS. The proposed study hypothesizes that these psychological and neurological factors increase the experience of experimentally-induced visceral pain in women with dysmenorrhea. Since dysmenorrhea, depression, and somatization are associated with abnormalities in frontocingulate networks, and given the emerging evidence supporting an association between affect and pain, it is necessary to account for the potential effects on regional brain function that may be associated with co-occurring psychological symptoms in individuals experiencing dysmenorrhea Advancing understanding regarding how psychological and physiological mechanisms confer risk for the development of chronic pelvic pain in the context of dysmenorrhea will contribute to informing the development of effective intervention strategies. The primary aims and hypotheses of the present study are as follows:

Study Hypotheses.

The present study had two objectives. The first objective was to characterize psychological factors and associated brain functioning in women suffering from dysmenorrhea and D+COS, respectively. It was hypothesized that compared to women

with dysmenorrhea, women with D+COS would demonstrate a) increased levels of brain activity as indexed by alpha, theta, and beta power (Hypothesis 1a), b) higher levels of somatization (Hypothesis 1b) and c) higher levels of depression (Hypothesis 1c).

The second objective was to examine the relationship between dysmenorrhea subtypes (i.e., dysmenorrhea and D+COS), resting state cortical activity, psychological factors, and experimental bladder pain. Specifically, it was predicted that women with D+COS would report higher levels of discomfort during experimentally induced visceral pain (Hypothesis 2a). For women with D+COS, increased pain levels during experimentally induced pain were expected to be mediated by increased levels of somatic symptoms, depression symptoms, and increased cortical activity (Hypothesis 2b).

CHAPTER TWO

METHOD

Participants

Female participants (ages 18 - 45; $M = 24.9$ years), were recruited by flyers posted on local college campuses, in the community, Craigslist advertisements, and by referral from gynecology clinics in our health system. Potential participants were instructed to call a study hotline number and complete a phone screen to determine eligibility. If eligible, participants were scheduled for an initial screening visit, during which self-report questionnaires on gynecological history, medical history, and mental health evaluations were administered.

Participants were asked to complete daily pain diaries to confirm menstrual pain and they were asked to abstain from using birth control pills for the duration of the study. Healthy controls had menstrual pain less than a two on a zero through ten self-report scale. Individuals with dysmenorrhea qualified for the study if their menstrual pain greater than five on a zero through ten self-report likert scale and confirmed with online daily diaries. (Casper, 1986). Participants were not eligible for the study if they met criteria for other pain conditions. After confirming study eligibility, participants were scheduled for a mid-luteal phase visit, approximately days 17-25 after commencement of menses. At the mid-luteal phase assessment visit, participants visit filled out additional

questionnaires and underwent several quantitative sensory testing (QST) measures described below. At the conclusion of the visit, participants were instrumented with a 32-channel electroencephalography (EEG) cap and performed brief tasks designed to measure physiological aspects of somatosensory amplification. The study was approved by the Institutional Review Board (IRB), and informed consent was obtained from each participant prior to performing any tests or filling out any questionnaires.

Materials and Procedure

The current study was approved by NorthShore University HealthSystem Institutional Review Board, and informed consent was obtained prior to participation. Participants were screened for eligibility, and those eligible were scheduled for an initial screening visit. Exclusion criteria for the study included: a) presence of active pelvic or abdominal malignancies, b) absence of regular menses, c) active genitourinary infection in the last four weeks, d) unable to read or comprehend the informed consent in English, e) unwilling to undergo pelvic examination/testing, f) presence of hypertension or risk for developing hypertension, g) unwilling to withdraw from oral contraceptives for two months prior to the study visit, h) inadequate visual acuity to identify 3mm letters on a monitor 1 m away, or i) hairstyles that precluded EEG cap placements. For the assessment session, participants were asked to avoid taking short-acting, over-the-counter analgesics (ibuprofen) and caffeine for at least six hours prior to arrival. Data were collected by trained research assistants. Individuals received monetary compensation for participation.

Reproductive-age women (18-45) with dysmenorrhea and D+COS were recruited. The following criteria were used to identify women with dysmenorrhea a) average menstrual pain $\geq$ 5/10 (0 = no pain and 10 = the worst imaginable pain) with menses or withdrawal uterine bleeding from cyclic oral contraceptives (OCs) without painkillers, b) menstrual pain in the region between the umbilicus and the perineum, above the level of the inguinal ligament and c) an indication the participant has attempted to resolve pain by medical means (including NSAIDs and/or OCs). Participants will complete a daily diary to verify menstrual pain during the screening period. They must have no concurrent chronic pain diagnoses that affect daily life or a history of more than 24 migraines per year. D+COS participants will meet the above mentioned criteria for dysmenorrhea, along with reporting >15 on a 0-100 visual analogue scale (VAS) for bladder pain during either first sensation or first urge at the assessment visit.

Measures

Demographics.

Participants responded to questions about demographic information, including their age and race/ethnicity.

Psychological and Health Variables.

Participants completed the Patient Reported Outcomes Measurement Information System (PROMIS) to evaluate depression and anxiety symptoms (α = 0.98; 0.97, respectively; Bartlett et al., 2015). The PROMIS depression scale consists of 28 items within a seven-day time frame and a five-point likert scale that ranges from one (Never) to five (Always; Cella et al., 2010; Pilkonis et al., 2011). Item content focuses on

emotional, cognitive, and behavioral manifestations of depression rather than somatic symptoms (i.e., fatigue, sleep, appetite). It was developed for use in both clinical and research settings.

Menstrual Pain Severity.

Participants were instructed to fill out daily diaries to eport their menstrual pain. Study data were collected and managed using REDCap electronic data capture tools hosted at NorthShore Health Systems. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources (Harris et al., 2009). This was done using a numeric rating scale where 0-no pain, 10-worst pain imaginable and also asked to describe any bleeding and list dose, type and use of painkillers. The participants were asked to fill out daily diary entries for all days between their screening visit and their first laboratory-based assessment.

<div align="center">

EEG Data Recording and Collection.

</div>

Participants are seated in a comfortable chair while EEG data is recorded with active electrodes using a standard 32-channel cap (EASYCAP, Germany). Electrode placement is based on the International 10-20 System (Jasper, 1958), with tin electrodes used for midline (Fz, Cz, Pz), left and right frontopolar (FP1, FP2), midfrontal (F3, F4), lateral frontal (F7, F8), central (C3, C4), anterior temporal (T3, T4), posterior temporal

(T5, T6), parietal (P3, P4), occipital (O1, O2), and mastoid (A1, A2) sites, with A1 as the reference for all other sites. Eye and facial movements were also recorded with electrodes placed about the right eye, below the left eye, and in the middle of the brow in order to account for ocular artifact rejecting of resting EEG data. All placement of electrodes and cap was implemented by a trained research assistant, and impedances were maintained below 25 kOhms. For online reference for the other sites on the cap, a left mastoid electrode (A1) was used. Data were recorded at a sampling rate of 500 Hz. EEG recordings were amplified by the BrainVision actiChamp amplifier and a 24 bit A/D converter.

EEG Data Reduction

EEG data were processed in Brain Electrical Source Analysis software (BESA Research 6.0). Automatic algorithms and visual inspection of the data were implemented to remove ocular and muscular artifact. An eye-movement correction program processed one second segments to remove EOG artifact from the EEG (Gratton, Coles, & Donchin, 1983; Miller, Gratton, & Yee, 1988), allowing retention of nearly all EEG epochs. The power spectrum, specifically alpha activity, was obtained by applying a Continuous Fast Fourier transform (FFT; Cooley & Tukey, 1965) on 1.024 second segments overlapping 50% for all of the electrode sites across all participants in EEGlab (Delorme & Makeig, 2004) producing spectral output in 0.488 Hz bins and then averaging all the power spectra across all artifact-free epochs within each sixty second baseline. A current source density (CSD) reference will be used as it is a spatial high-pass filter that is relatively insensitive to deeper and more distributed sources. Further, past findings have indicated

that CSD-transformed frontal EEG asymmetry at rest may be a robust marker of risk for

depression, and may be advantageous for examining stable trait estimates of frontal EEG

asymmetry (Stewart, Coan, Towers, & Allen, 2014; Koo, Thome, Berger, Foley, &

Hoeppner, 2015). Theta, alpha, and beta power (4-7, 8-13, and 14-30 Hz, respectively)

was extracted from the power spectrum in 0.977-Hz bins. Electrode Fz was selected for

analyses as a proxy for frontal activity.

CHAPTER THREE

RESULTS

Hypothesis Testing

Objective 1.

The first objective of this study was to characterize psychological factors and

associated brain functioning in women suffering from dysmenorrhea and D+COS,

respectively. 63 women (see Table 1) were included in the present study. The

experimental bladder pain, the outcome variable in Objective 2, produced a significant

violation of the assumption of normality, failing test for bimodality. A Shapiro-Wilks test

was used to test for normality on the main dependent variable, bladder pain. Before

transforming, the data indicated it was not normally distributed in both groups ($W(69) =$

0.73, $p <.001$). After taking the log of bladder pain, the distribution was much more

normalized ($W(69) = 0.95$, $p = .01$). Doing so improved the skewness of the data, thus

making a Type 1 Error less likely.

Pearson correlations were run to examine the correlations among the

psychological, physiological and pain variables across the sample (see Table 2).

Experimentally induced bladder pain was correlated with menstrual pain, somatic

symptoms, and beta oscillatory activity. Menstrual pain was correlated with somatization,

Table 1. Group means for study variables. The means (sd) for study variables across the two groups.

Variable	Dysmenorrhea (N=35)	Dysmenorrhea + COS (N=28)
Age (years)	23 (5)	26 (6)
Bladder Pain	1.2 (1.3)	2.3 (1.5)
Menstrual Pain	3.3 (1.7)	4.6 (2.0)
Somatization	1.7 (1.7)	2.9 (2.7)
Depression	51.2 (8.6)	52.0 (9.0)
Frontal Alpha Power	-5.33 (0.63)	-5.31 (0.64)
Frontal Theta Power	-4.29 (0.49)	-4.37 (0.62)
Frontal Beta Power	-6.25 (0.77)	-6.21 (0.48)

Table 2. Correlation matrix of study variables. Correlations across the sample. Significant correlations ($p < 0.05$) are designated with an asterisk.

	1	2	3	4	5	6
1. Bladder Pain						
2. Menstrual Pain	**0.30***					
3. Somatization	**0.43***	**0.25***				
4. Depression	-0.01	-0.12	**0.35***			
5. Frontal Alpha Power	0.08	-0.14	0.08	**0.27***		
6. Frontal Theta Power	-0.07	-0.10	-0.08	-0.13	**0.40***	
7. Frontal Beta Power	**0.26***	-0.00	-0.08	0.23	**0.43***	0.21

and somatization was correlated with depression. Alpha activity was positively correlated with depression symptoms, replicating previous research.

   Hypotheses 1a, 1b &1c. Three two-tailed independent samples t-tests were run to test whether increased levels of brain activity (i.e., as indexed by alpha, theta, and beta power) would be observed in women with D+COS compared to women who have dysmenorrhea but not COS. There were no significant differences between groups (see Table 3). Compared to women with dysmenorrhea, women with D+COS were hypothesized to report higher levels of somatic and depressive symptoms. Results showed the D+COS group had significantly higher somatic symptoms ($t(61) =$-3.5$, p$ $=$.04$), and depression levels were not different between groups (see Table 3).

Objective 2.

   The second objective was to examine the relationship between dysmenorrhea subtypes (i.e., dysmenorrhea and D+COS), resting state cortical activity, psychological factors, and experimental bladder pain. Since only beta activity was significantly correlated with experimental bladder pain, theta and alpha were dropped from further analyses.

Table 3. *t*-test comparing dysmenorrhea and D+COS groups. *t*-test (*df* = 61) results comparing dysmenorrhea and D+COS groups on psychological, physiological, and pain symptoms.

Outcome		
	t	*p*
Frontal Alpha Activity	-0.08	0.80
Frontal Theta Activity	0.55	0.85
Frontal Beta Activity	-0.24	0.53
Somatization	2.06	**0.04**
Depression	-0.35	0.73
Bladder Pain	3.10	**<0.01**

Hypothesis 2a. An independent sample t-test was run to test whether women with D+COS would report higher levels of discomfort during experimentally induced visceral pain. Results showed the D+COS group had significantly higher levels of experimental bladder pain ($t(59) = -3.1, p < .01$).

Hypothesis 2b. For women with D+COS, increased pain levels during experimentally induced pain were expected to be mediated by increased levels of somatic and depression symptoms, and increased cortical activity (i.e., beta). An omnibus parallel mediation model (Figure 1) was used in order to evaluate this hypothesis. To test this model, group was entered as the predictor variable, somatization, depression, and beta activity were entered as parallel mediators, and experimental bladder pain was entered as the dependent variable. Bootstrapping was implemented ($k = 10,000$) to test the indirect effects. Group was not a significant predictor of somatization (path a_1), depression (path a_2), or frontal beta activity (path a_3) (see Table 4). Group (path c'), somatization (path b_1), depression (path b_2), and frontal beta activity (path b_3) were all significant predictors of

experimental bladder pain (Table 4). There was a negative relationship between depression (path b_2) and visceral pain, and relationships among the other variables were positive. Together the four predictors accounted for 38.8% of the variance in predicting bladder pain (see simultaneous regression model included in Table 3). Results from the parallel mediation analysis illustrate that women with D+COS experience more experimental visceral pain via increased somatic symptoms (Table 5). While depression and frontal beta activity were significant predictors of experimental bladder pain (Table 3), they were not significant mediators (see Table 4).

Figure 1. Statistical Diagram of Parallel Multiple Mediator Model. Statistical diagram of parallel multiple mediator model (with three mediators: somatization, depression, frontal cortex beta power). The diagram shows A) the total effect of group on experimental bladder pain and B) the direct effect and causal pathways associating group with experimental bladder pain.
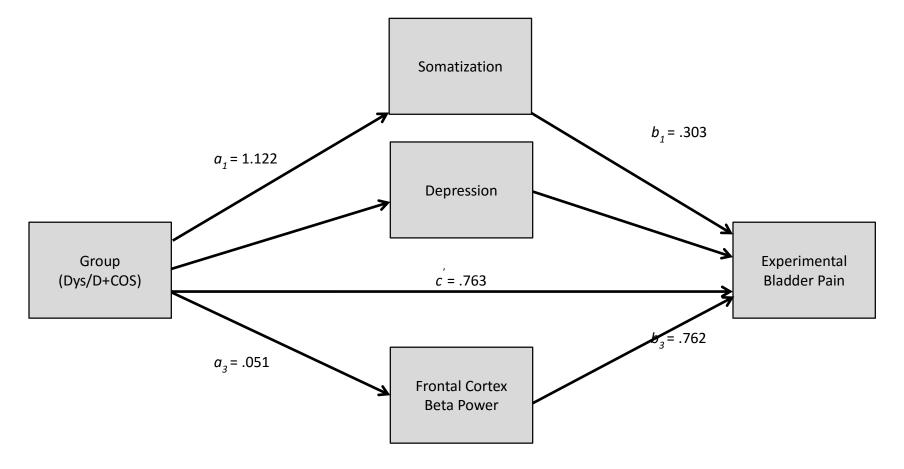
Table 4. Parallel Multiple Mediation Model. Regression coefficients, standard errors, and model summary information for the parallel multiple mediator model depicted in Figure 1

		Consequent													
		Somatization (BSI) (M_1)				Depression (M_2)				Frontal Beta (M_3)				Experimental Bladder Pain (Y)		
Antecedent		Coeff.	SE	p		Coeff.	SE	p		Coeff.	SE	p		Coeff.	SE	p
(X) Group	a_1	1.220	.578	.057	a_2	.820	2.308	.724	a_3	.051	.166	.758	c'	.763	.319	.020
(M1) Somatization		—	—	—		—	—	—		—	—	—		.303	.075	.002
(M2) Depression		—	—	—		—	—	—		—	—	—		-.044	.019	.026
(M3) Frontal Beta Power		—	—	—		—	—	—		—	—	—		.762	.252	.004
Constant	i_{M1}	1.686	.377	.000	i_{M2}	51.26	1.507	.000	i_{M3}	-6.247	.108	.000		7.751	2.056	.0004
		$R^2 = .060$ $F(1, 59) = 3.77, p = .057$				$R^2 = .002$ $F(1, 59) = .123, p = .724$				$R^2 = .002$ $F(1, 59) = .096, p = .758$				$R^2 = .388$ $F(4, 56) = 8.889, p < .0001$		

Table 5. Direct and Indirect Effects of OLS Regression. Direct effect and Indirect effects using 95% bias-corrected confidence intervals from OLS regression predicting Experimental Bladder Pain Scores. The indirect effect ($a_1 b_1$) for somatization is significant since zero is not included in the confidence interval (CI).

	Effect	Lower CI	Upper CI
Indirect effects			
$a_1 b_1$	0.35	0.135	0.767
$a_2 b_2$	-0.04	-0.315	0.170
$a_3 b_3$	0.04	-0.190	0.323
Direct effect (c')	0.76	0.123	1.402s

CHAPTER FOUR

DISCUSSION

Our results provide evidence that psychological symptoms and brain activity are related to increased levels of visceral pain, specifically for women with dysmenorrhea and cross-organ sensitization (COS). Results from the parallel mediation model showed that psychological and physiological factors (i.e, somatization, depression, and frontal beta activity) are related to experimental visceral pain; however, somatization was the only significant causal link between women suffering from D+COS and bladder pain. Somatic symptoms are thus a candidate risk factor for developing chronic pelvic pain in women with dysmenorrhea. It is critically important that somatic symptoms should be considered a primary target for prevention and intervention strategies.

Although the predicted relationship between depression and frontal alpha was observed, and depression was correlated with somatization, depression did not emerge as a significant causal factor related to visceral pain in the omnibus model. The presence of increased frontal alpha during resting state has been theorized to be a risk factor for depression, suggesting that many of the women in the present sample are likely at high risk for depression. If visceral pain increases over time, depression symptoms may also increase. Longitudinal data are important for resolving whether depression symptoms become a significant contributor to visceral pain as the duration of dysmenorrhea-related symptoms continue. Future directions include following this sample longitudinally in

order to better understand the directionality of the relationships between psychological symptoms, neural correlates, and physical pain perception in women with dysmenorrhea.

Although the present study advanced the characterization of the psychological and physiological factors associated with visceral pain in women with dysmenorrhea, some limitations do exist. The use of cross-sectional data limits our ability to fully understand the developmental trajectory of pain outcomes in women with dysmenorrhea. In particular, the role of depression symptoms with regard to pain outcomes may be better understood with longitudinal data. Although the data are cross-sectional, this not preclude the use of mediation analyses (Hayes, 2013). Mediation analyses are commonly implemented with cross-sectional data in order to advance theory-driven hypotheses (Hayes, 2013). Longitudinal data will be useful in confirming the results from the present study which indicate that increased somatic symptoms are a causal factor for women with D+COS who experience high levels of experimentally-induced bladder pain. Furthermore, longitudinal data will be necessary to understand whether somatic symptoms onset prior to COS, or whether COS causes the onset of somatic symptoms.

Further, more data is needed to understand the generalizability of these results. The present study sample consists primarily of young adult women, and data from a larger spectrum of women is needed to developmentally characterize the effects of dysmenorrhea and D+COS across all age ranges. Additionally, this study used 32-channel EEG equipment to measure brain activity, and thus source analyses cannot be computed in order to validate that beta measured at electrode Fz is generated from the

frontal regions below the electrode in this sample. Additional research with high-density EEG is warranted.

Currently, dysmenorrhea is commonly treated with NSAIDS and other anti-inflammatory drugs, which may not be effectively ameliorating psychological and physiological factors. Considering the observed association with psychological factors as well as increased brain activity, a more holistic treatment strategy approach may be more effective. By treating not only physical symptoms associated with visceral pain, but also somatic symptoms, women with dysmenorrhea and D+COS may be more effectively treated. Notably, mindfulness exercises have been effective in not only reducing chronic pain, but also decreasing the likelihood of prolonged somatic symptoms (Kabat-Zinn, Lipworth, & Burney, 1985). Mindfulness may aid in filtering inputs to the primary somatosensory cortex, which could broaden attentional resources that may be narrowly focused on pain and shift that concentration on awareness of the body in a nonjudgmental way (Kerr, Sacchet, Lazar, Moore, & Jones, 2013). Since dysmenorrhea, depression, and somatization are associated with abnormalities in frontocingulate networks, and given the evidence supporting an association between affect and pain, understanding the multidimensionality of dysmenorrhea-related symptoms from an interdisciplinary perspective is imperative in developing effective treatments. Continuing to work toward identifying potentially modifiable psychological and physiological risk factors is critical to ameliorating the development of chronic pelvic pain in the context of dysmenorrhea.

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