The Role of Attention, Catastrophizing, and Anxiety in the Experience of Chronic Pain: Imaging Pain in Women With and Without Vestibulodynia

By

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Abstract

Provoked Vestibulodynia (PVD) is the most common form of chronic vulvar pain, affecting 12% of women in the general population. Research has demonstrated that women with PVD display both allodynia and hyperalgesia to pain at vulvar and non-vulvar sites, as well as reduced psychosocial functioning. The goal of this study was to use a multi-method approach (interview, questionnaires, sensory testing, and fMRI) to examine group differences between women with PVD (N=15) and healthy control women (N=15). Results will allow for improved understanding of the interaction between psychosocial and neurobiological underpinnings of this disorder, which can contribute to the creation of better treatment strategies. Variables included psychophysical and psychosocial measures, as well as neural activations associated with painful pressure, painful words, and psychosocial functioning. Differences between subgroups of PVD, based on temporal onset, were also examined. There were no robust group differences in neural activation during the application of pain or pain words. This finding is consistent with many studies that match groups on pain intensity ratings, as opposed to amount of pressure applied. Painful pressures and painful words resulted in greater neural activation than neutral words or touch; however, there were no group differences for the word conditions. Women with PVD reported increased psychosocial dysfunction, including higher levels of anxiety and catastrophizing. Significant correlations were found between these psychosocial variables and areas of the brain associated with pain modulation and attention (e.g., PFC). Examination of PVD subgroups revealed differences in neural correlates of anxiety and catastrophizing during painful stimulation. This finding adds to the literature suggesting that women with primary PVD experience greater dysfunction than women with secondary PVD. Overall, these studies support findings of pain processing in the general pain literature, as well as supporting PVD as a chronic pain condition. They also add to the development of a greater understanding of the interaction between psychophysical and psychosocial components of chronic pain by examining their relationship with neural activations. Future research should examine brain functioning in
PVD women pre- and post-treatment as well as examining neural correlates of other psychosocial variables that contribute to the pain experience (e.g., somatization).
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<tbody>
<tr>
<td>APA</td>
<td>American Psychological Association</td>
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<tr>
<td>ACC</td>
<td>Anterior cingulate cortex</td>
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<tr>
<td>DLPFC</td>
<td>Dorsolateral prefrontal cortex</td>
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<td>DMN</td>
<td>Default mode network</td>
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<tr>
<td>FM</td>
<td>Fibromyalgia</td>
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<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
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<tr>
<td>IC</td>
<td>Insular cortex</td>
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<td>IPL</td>
<td>Inferior parietal lobe</td>
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<tr>
<td>MCC</td>
<td>Middle cingulate cortex</td>
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<tr>
<td>OFC</td>
<td>Orbitofrontal cortex</td>
</tr>
<tr>
<td>PFC</td>
<td>Prefrontal cortex</td>
</tr>
<tr>
<td>PPT</td>
<td>Pressure pain threshold</td>
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<tr>
<td>PVD</td>
<td>Provoked vestibulodynia</td>
</tr>
<tr>
<td>QST</td>
<td>Quantitative sensory testing</td>
</tr>
<tr>
<td>S1</td>
<td>Primary somatosensory cortex</td>
</tr>
<tr>
<td>S2</td>
<td>Secondary somatosensory cortex</td>
</tr>
<tr>
<td>SMA</td>
<td>Supplementary motor area</td>
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<tr>
<td>SMG</td>
<td>Supramarginal gyrus</td>
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<td>SVC</td>
<td>Small volume correction</td>
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Pain is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey, Lindblom, Mumford, & Sunderland, 1994, p. 210). Acute pain is adaptive and necessary for survival; however, pain can also be chronic and maladaptive (Woolf, 2004). Provoked Vestibulodynia (PVD) is an example of a chronic pain condition. It is characterized by pain elicited at the vulvar vestibule in response to pressure. PVD is characterized by pain that is “burning” and “sharp” in quality. The pain of PVD is experienced in the absence of identifiable tissue damage, thus it is often diagnosed based on self-reported symptoms in combination with a cotton-swab test of the vulvar vestibule (see below; Pukall, Binik, & Khalifé, 2004). This condition is estimated to have a lifetime prevalence of up to 12% in the general population (Harlow & Stewart, 2003). Onset can be from the first penetration attempt (termed primary) or can develop after a period of pain-free penetration (termed secondary).

Both the biological and psychosocial aspects of pain need to be examined in order to fully understand a pain condition (Gatchel, Bo Peng, Peters, Fuchs, & Turk, 2007). Research has substantiated multiple psychosocial effects of PVD, including reduced sexual functioning, lower levels of sexual self-efficacy, and increased pain-related anxiety and catastrophizing (Arnold, Bachmann, Rosen, Kelly, & Rhoads, 2006; Bergeron, Pukall, & Binik, 2005; Danielsson, Sjoberg, & Wikman, 2000; Gates & Galask, 2001; Meana, Binik, Khalifé, & Cohen, 1997; Nunns & Mandal, 1997; Payne, Binik, Amsel, & Khalife, 2005; Pukall, Binik, Khalifé, Amsel, & Abbott, 2002; Pukall, Lahaie, & Binik, 2005b; White & Jantos, 1998). Psychophysical testing has revealed that, at the vulvar vestibule, women with PVD experience pain in response to stimuli that are not typically painful (i.e., allodynia). They also have an increased pain response to already painful stimuli (i.e., hyperalgesia). In addition, studies have demonstrated that the heightened sensitivity is present at areas distal to the vulva: women with PVD are not only more sensitive to stimuli at the vulvar vestibule, but also at other, non-painful body sites (e.g., Giesecke, Reed, Haefner,
Giesecke, Clauw, Gracely, 2004; Pukall et al., 2002). These findings have been interpreted to indicate that PVD entails some dysregulation at the level of the central nervous system. Supporting this idea are two neuroimaging studies demonstrating both anatomical and functional changes in women with PVD as compared with non-affected women. These studies have found increased grey matter density in brain areas related to pain modulation and stress (Schweinhardt, Kuchinad, Pukall, & Bushnell, 2008), and increased activation in areas of the brain referred to as the ‘pain matrix,’ which occurs during both mild and moderate pain applications (Pukall, Strigo, Binik, Amsel, Khalifé, & Bushnell, 2005).

In various chronic pain conditions, pain stimulation, regardless of modality (e.g., thermal, pressure, electrical), generally activates regions in the lateral (sensory-discriminative) and medial (cognitive-evaluative, and affective-motivational) areas of the pain matrix. The most commonly activated regions in the pain matrix include the somatosensory cortices (S1 & S2), the thalamus, the insular cortex (IC), the prefrontal cortex (PFC), and the anterior cingulate cortex (ACC; Apkarian, Bushnell, Treede, & Zubieta, 2005). The pain matrix is also associated with stimulus saliency; the amount of attention an individual pays to a particular stimulus (e.g., hypervigilance) is intimately intertwined with the pain response. This increased focus, or attention, to pain is hypothesized to result in pain amplification (Lethem, Slade, Troup, & Bentley, 1983; Vlaeyen & Linton, 2000). Such amplification of pain may occur by altering central thresholds of excitability over time, and eventually increasing one’s sensitivity to pain by activating a brain network thought to be associated with stimulus novelty and salience, which overlaps with the pain matrix (Legrain, Iannetti, Plaghki, & Mouraux, 2011; Melzack, 1999). In addition to attention, the fear-avoidance model suggests that catastrophizing, avoidance, and anxiety/fear of pain are also hypothesized to play a role in the amplification of pain (Vlaeyen & Linton, 2000). When studies examine levels of psychosocial functioning within a particular chronic pain group or in healthy individuals, psychosocial functioning is correlated with neural activation (e.g., Seminowicz & Davis, 2006). Individuals with chronic pain, however, tend to fare worse than healthy controls, and it has been demonstrated by numerous studies that differences in neural activation between healthy participants and
chronic pain participants is due in part to the important role of the psychosocial context in the modulation of pain intensity, especially in chronic pain populations (e.g., Campbell & Edwards, 2009; Edwards, 2005; Keefe, Rumble, Scipio, Giordana, & Perri, 2004; Schweinhardt, Kuchinad, Pukall, & Bushnell, 2008; Turk & Okifuji, 2002). Interestingly, findings of differences in neural activation between chronic pain groups and healthy control participants tend to be limited to studies in which equal levels of stimulation are applied (e.g., both groups receive a thermal stimulus of 45 degrees Celsius). When subjective ratings are held constant between groups, chronic pain patients and controls show few differences in neural activation for pain.

The present study aimed to expand upon research on women with PVD by examining the neural effects of painful and non-painful sensations in these women as compared with healthy control women. The current study controlled for pain intensity ratings, rather than for stimulus intensity, as matched stimulus intensity has been previously researched in this group (Pukall et al., 2005). Demographic, psychosexual, and psychophysical data were collected in order to examine whether group differences in the current sample replicate those reported in the literature, and to allow for comparison between the current PVD group and other pain populations in the literature.

Three primary research questions were examined. The first study examined differences in neural activation between painful and non-painful word primes during various types of pressure stimuli (painful and non-painful). The word stimuli were intended as a measure of the effect of attention on pain processing. It was hypothesized that painful words, which draw attention to their pain, would result in greater activation of the pain matrix than would neutral words and that the difference in activation between painful and neutral words would be greater for women with PVD as compared with control women. It was also hypothesized that, for both groups, painful pressure would result in greater activation than non-painful pressure, which would result in greater activation than no pressure.

The second study examined the correlations between neural activation and psychosocial measures, specifically, anxiety and pain-related catastrophizing. It was hypothesized that brain areas
involved in pain processing, particularly areas associated with affective processing, would be correlated with the psychosocial variables, with positive correlations in medial pain areas such as the insula and ACC, and negative correlations in areas of the pre-frontal cortex (Semenowicz & Davis, 2006). This is the first study to examine correlates of functional neural imaging and psychosocial variables in women with PVD, to the best of the author’s knowledge. A previous study examining grey matter density in women with PVD found that vulvar pain catastrophizing scores correlated positively with grey matter density in the hippocampus, para-hippocampus, and substantia nigra regions, areas that play a role in pain modulation (Schweinhardt et al., 2008). Neuroanatomical changes in regions of the basal ganglia, including the substantia nigra, have been hypothesized as being associated with problems in endogenous pain modulation and may help to explain both generalized and localized pain sensitivity in chronic pain patients (Schweinhardt et al., 2008).

The third study examined differences between women with primary and secondary PVD, as previous research has suggested that these two subtypes may differ in terms of etiological and maintaining factors (e.g., Babula, Linhares, Bongiovanni, Ledger, & Witkin, 2008; Burrows, Klingman, Pukall, & Goldstein, 2008). It was hypothesized that women with primary PVD would demonstrate poorer psychosocial functioning, higher pain sensitivity, and greater activations across the pain matrix, as compared to women with secondary PVD.

Findings from the current studies provide further evidence of the interaction of biological and psychosocial factors in chronic pain, as well as evidence for the role of centrally-acting treatments (e.g., medications, cognitive behavioural therapy) for women with PVD, particularly for women with primary PVD.
Chapter 2. Literature Review

2.1. Vulvodynia

While for many women the words ‘sexual intercourse’ are associated with the experience of pleasure, for some women these words (and the actual experience of intercourse itself) are associated with intense pain. The most common diagnosis of this pain is broadly termed vulvodynia, a condition defined by the International Society for the Study of Vulvovaginal Disease (ISSVD) as “vulvar discomfort, most often described as burning pain, occurring in the absence of relevant visible findings or a specific, clinically identifiable, neurologic disorder” (Haefner, 2007, p. 49). There are two main subtypes of vulvodynia: generalized vulvodynia (GVD) and provoked vestibulodynia (PVD). These two subtypes can occur independent of one another, or they can co-exist. The subtypes are based on the location and temporal pattern of the pain. The pain of GVD affects the entire vulvar region, and it is usually spontaneous and constant. It can be exacerbated by activities that involve pressure to the affected region (e.g., gynecological exams, bicycle riding, sexual activity). The pain of PVD, on the other hand, is highly localized to the vulvar vestibule (i.e., vaginal opening) and is provoked by pressure.

There have been a number of studies examining the prevalence of vulvodynia, and estimates in community samples range from a cross-sectional prevalence of 1.7% to 12%, and a lifetime prevalence of 3% to 16% (Arnold, Bachmann, Rosen, & Rhoads, 2007; Harlow, Wise, & Stewart, 2001; Harlow & Stewart, 2003; Reed, Crawford, Couper, Cave, & Haefner, 2004; Reed et al., 2012). In clinical samples (i.e., samples obtained from women presenting to physician offices), the prevalence is as high as 34% (Berglund, Nigaard, & Rylander, 2002). Prevalence rates vary based on the stringency of criteria used in defining vulvodynia (e.g., duration of pain, sampling techniques). Some studies have shown that between 1 out of 20 and 1 out of 50 women develop symptoms of vulvodynia each year (Reed, Haefner, Sen, & Gorenflo, 2008; Sutton, Bachmann, Arnold, Rhoads, & Rosen, 2008), resulting in more than one million new cases of vulvodynia in the United States each year. To date, there have been no epidemiological...
studies examining the prevalence of chronic vulvar pain in Canadian women. Vulvodynia affects women of all ethnicities (Harlow & Stewart, 2003). Although women of all ages may experience short-lived dyspareunia (i.e., pain with intercourse), chronic pain at the vaginal opening (the PVD subtype) affects a disproportionate number of young women (Friedrich, 1987; Levy, Hynan, & Hayley, 2007; Rogstat, 2000). In addition, Jantos and Burns (2007) found that 75% of a sample of 744 women diagnosed with any type of vulvodynia was under the age of 34. The average age of onset of this sample was 22.8 years. While decreased sexual satisfaction and sexual functioning are prevalent among women with vulvodynia (Arnold et al., 2006; Hallam-Jones, Wylie, Osborne-Cribb, Harrington, & Walters, 2001; Jantos & Burns, 2007), they also experience problems in relationship functioning (Davis & Reissing, 2007), mental health (Jantos & White, 1997; Masheb, Wang, Lozano, & Kerns, 2005; Wylie, Hallam-Jones, & Harrington, 2004), and physical health (Reed et al., 2000). Vulvodynia patients also report a reduced quality of life (Ponte, Klemperer, Sahay, & Chren, 2009), with 42% reporting that they feel “out of control” of their lives and 60% stating that they feel “out of control” of their bodies (Arnold et al., 2006). Quality of life is reduced in all patients with chronic pain conditions, though research on a heterogeneous sample of pain patients found that those with low back pain or conditions with multiple pain sites experienced the lowest quality of life (Lamé, Peters, Vlaeyen, Kleef, & Patijn, 2005). The significant association between vulvodynia and other chronic pain conditions, such as fibromyalgia, irritable bowel syndrome (Arnold et al., 2006), and interstitial cystitis (Reed et al., 2012) results in comorbidities that also contribute to reductions in quality of life. Despite the negative impact of vulvar pain on the sexual and non-sexual domains of affected women’s lives, studies have found that only about 50% of women with vulvar pain seek treatment (Harlow & Stewart, 2003; Sutton, 2007). This discrepancy is likely due to the often sexual nature of the pain; indeed, many women are reluctant to discuss sexual issues with healthcare providers, and many healthcare providers are reluctant to ask their patients (Berman et al., 2003; Sobecki, Curlin, Rasinski, & Tessler-Lindau, 2012). Of the affected women who do seek treatment, however, about 40% do not receive a diagnosis despite multiple consultations
(Harlow et al., 2001). Approximately 29% of Harlow and colleague’s (2001) sample sought consultation with five or more healthcare professionals, and the average number of healthcare professionals sought out by treatment-seeking patients in Sutton’s (2007) group was two. These statistics reflect the lack of medically-related knowledge regarding this common and chronic condition. In a study examining management of vulvar pain by clinicians, 85% of respondents indicated that vulvodynia was not adequately addressed in their training (Updike & Wiesenfeld, 2005).

2.2. **Provoked Vestibulodynia**

2.2.1. **Diagnosis**

Provoked Vestibulodynia (PVD; formerly Vulvar Vestibulitis Syndrome) is the most common subtype of vulvodynia. PVD is characterized by provoked pain localized to the vulvar vestibule (i.e., the vaginal entrance; Friedrich, 1987), which is usually described as “burning” and “sharp”. The diagnosis of PVD is based on a combination of patient self-report of pain during sexual intercourse and a positive (i.e., painful) response to a cotton-swab test, during which areas of the vulva are palpated with a cotton-swab to assess tenderness to pressure (Pukall, Binik, & Khalifé, 2004; see Methods Section). The original diagnostic criteria consisted of: 1) severe pain upon vestibular touch or attempted vaginal entry; 2) tenderness to pressure localized to the vulvar vestibule; and 3) physical findings limited to the presence of vestibular redness (Friedrich, 1987). The latter criterion (i.e., redness) is no longer a requirement for the diagnosis, as it has not been reliably demonstrated (Bergeron, Binik, Khalifé, Pagidas, & Glazer, 2001; Masheb, Lozano, Richman, Minkin, & Kerns, 2004).

2.2.2. **Primary versus Secondary PVD**

The pain of PVD can be present since the woman’s first penetration attempt (termed primary PVD) or it can develop after a period of pain-free penetration (termed secondary PVD). The prevalence of these two different temporal onsets is thought to be about equal (Goetsch, 1991); however, the subtypes appear to be characterized by different demographic and pain variables. Women with primary PVD are
more likely to be nulliparous (i.e., have never had children) and to be single in terms of relationship status (Bornstein, Maman, & Abramovici, 2001; Witkin, Gerber, & Ledger, 2002). They also report more severe pain with first intercourse and subsequent intercourse attempts (Goetsch, 1991; Sutton et al., 2009), dysmenorrhea (Granot, Friedman, Yarnitsky, Tamir, & Zimmer, 2004a), and a family history of dyspareunia (Goetsch, 1991). When compared to women with secondary PVD, women with primary PVD report heightened anxiety around body exposure during sexual activity, as well as lower levels of social and emotional functioning (Sutton, Pukall, & Chamberlain, 2009). In addition, women with secondary PVD typically do not display the same degree of pain sensitivity as women with primary PVD. For example, women with primary PVD displayed lower heat pain tolerance at a non-vulvar site, as well as lower heat detection and heat pain thresholds at the vulvar vestibule (Sutton et al., 2009). These groups also differ in treatment response (see below). Given these differences, it has been proposed by a number of researchers that the two subtypes may develop from different etiological pathways (Goetsch, 1991; Granot et al., 2004a). One study suggested that women with primary PVD may have developed vulvar pain as a result of a congenital neuronal hyperplasia in urogenitally derived tissue, suggesting that their pain may be due to an increase in nerve fibers at the vulvar vestibule (Burrows et al., 2008). Another study reported that primary PVD may develop due to an MBL*B gene polymorphism combined with an environmental trigger, such as friction with penetration (Babula et al., 2008). Despite similar levels of inflammation, women with primary PVD also have significantly more neural hypertrophy (i.e., enlargement of cells) and hyperplasia (i.e., increase in number of cells) at the vulvar vestibule, as well as increased progesterone receptors, even after controlling for duration of symptoms and age (LeClair, Goetsch, Korcheva, Anderson, Peters, & Morgan, 2011). Despite these noted differences, most researchers continue to study women with PVD as a homogenous group; that is, they do not take the onset of the pain into account when analyzing their data.
2.2.3. **Etiology**

It is hypothesized that many factors play a role in this condition. As with many chronic pain conditions, PVD may stem from and be maintained by a complex combination of factors, including local changes to the vestibular mucosa, changes in the pelvic floor musculature, central pain sensitivity (Zolnoun et al., 2006), and psychosocial factors. The initial research on PVD implicating local inflammatory or dermatological causes has not been consistently supported by research (Lundqvist, Hofer, Olofsson, & Sjoberg, 1997). Genetic studies, however, have demonstrated that women who carry pro-inflammatory genetic variants are 4.0-8.5 times more likely to develop PVD (Foster, Sazenski & Stodgell, 2004). Women with PVD also have less potent anti-inflammatory genetic variants (Foster & Stodgell, 2004). Chronic inflammation results in local changes at the vulvar vestibule, including neuronal proliferation and elevation of pro-inflammatory substances (Bohm-Starke et al., 1998; 2001). These changes include increased C-afferent nociceptors in the vestibular mucosa of women with PVD (Bohm-Starke, Hilliges, Falconer et al., 1998) and regional elevations of pro-inflammatory cytokines (cell-signaling protein molecules), which are produced by fibroblast strains (Foster, Piekarz, Murant, LaPoint, Haidaris, & Phipps, 2007). Pro-inflammatory substances activate inflammatory cells, such as neuroendocrine and mast cells. For example, an increased number of mast cells in women with PVD may occur as a result of an allergen, including topical creams or seminal fluid (Babula et al., 2004; Bornstein et al., 2008). In addition to allergens, local changes can be provoked by the repeated presence of yeast (Farmer et al., 2011), tissue/neuronal injury, and hormonal changes (Eva, Maclean, Reid, Rolfe, & Perrett, 2003). Hormonal causes have also been supported by research findings suggesting increased risk of developing PVD in women who use hormonal contraceptives (Bohm-Starke, Johannessen, Hilliges, et al., 2004; Greenstein, Ben-Aroya, Fass et al., 2007). Overall, the sensory thresholds of the vestibular mucosa are lowered, and continued inflammation can eventually lead to central sensitization (Gracely, Lynch, & Bennett, 1992).
Musculoskeletal causes have also been hypothesized, with much research to support the role of pelvic floor dysfunction in women with PVD. Studies using surface electromyography (sEMG) of the pelvic floor (Glazer, Jantos, Hartmann, & Swencionis, 1998; White, Jantos, & Glazer, 1997) and pelvic floor examinations by physical therapists who were blinded to participant status (Reissing, Brown, Lord, Binik & Khalifé, 2005) have found that women with PVD can be differentiated from a control group, with findings of greater hypertonicity of the vagina, lack of vaginal muscle strength, and restricted vaginal opening in the PVD group. Another study found that only sEMG activity in the superficial pelvic floor muscles, but not the deep pelvic floor muscles, differentiated women with PVD from control women (Gentilcore-Saulnier, McLean, Goldfinger, Pukall, & Chamberlain, 2010). Women with PVD demonstrate greater vaginal hypertonicity, reduced vaginal muscle strength, reduced pelvic floor muscle flexibility, reduced relaxation and resting state of the pelvic floor muscles, and greater restriction of the vaginal opening (Gentilcore-Saulnier et al., 2010; Reissing et al., 2005).

A multitude of other studies from various research groups have also found results implicating involvement of the central nervous system in PVD. Not only do women with PVD show increased sensitivity at the vulvar vestibule as compared to control women, but this finding also holds true in non-vulvar areas of the body (Giesecke et al., 2004; Granot, Friedman, Yarnitsky, & Zimmer, 2002; Pukall et al., 2002). Central nervous system dysregulation is also supported by two neuroimaging studies of women with PVD. A study of structural brain differences between women with PVD and control women found increased grey matter density in brain areas related to pain modulation and stress (Schweinhardt et al., 2008), while a functional neuroimaging study found augmented neural activation in women with PVD for both mild and moderate painful pressures applied to the vulvar vestibule. This augmented activation was found in brain regions associated with pain processing (Pukall et al., 2005).
2.2.4. Psychosocial Functioning

Early literature on vulvar pain often cited sexual abuse as a potential etiological mechanism; however, the literature on sexual abuse and PVD is equivocal, with the majority of studies finding no relationship between sexual abuse and PVD. A self-administered survey found that women with PVD were more likely to report poor family support, physical, and sexual abuse histories as compared to control women; however, the authors themselves noted that replication was required given the inconsistencies in the literature (Harlow & Stewart, 2005). Other research groups have found that women with vulvodynia were significantly less likely to report a history of sexual abuse and/or severe psychological disturbances as compared with a chronic pelvic pain group (Bodden-Heidrich et al., 1999) and that their report of sexual abuse history was similar to that of asymptomatic controls (Reed, Haefner, Punch, Roth, Gorenflo, & Gillespie, 2000). Other studies support findings suggesting that the incidence of sexual abuse is not more common in women with vulvodynia as compared with control groups (e.g., Plante & Kamm, 2008; Schover, Youngs, & Cannata, 1992).

Not only is there a diverse number of ways in which psychosocial factors can influence or contribute to the above noted potential etiological mechanisms, there are also many psychosocial maintaining factors for pain, resulting in a wide variety of domains in which women with PVD (and their partners) are affected. Not surprisingly, women with PVD report reduced sexual functioning as compared with healthy control women (e.g., Desrochers, Bergeron, & Landry, 2008). They also report more problems with their intimate relationships (Jodoin et al., 2011; Plante & Kamm, 2008; Smith & Pukall, 2011), a common finding in chronic pain patients (e.g., Cano, Johansen, Leonard, & Hanawalt, 2005; Flor, Turk, & Scholtz, 1987). Also consistent with patients with other chronic pain conditions, women with PVD report reduced psychosocial functioning including hypervigilance associated with pain, higher levels of pain catastrophizing, higher somatization scores, higher levels of state and trait anxiety, and lower levels of sexual self-efficacy as compared with control participants (Arnold et al., 2006; Bergeron et al., 2005; Danielsson et al., 2000; Gates & Galask, 2001; Masheb, Wang, & Lozano, 2005; Meana et
al., 1997; Nunns & Mandal, 1997; Payne et al., 2005; Pukall et al., 2002; Pukall et al., 2005b; White & Jantos, 1998). The relationship between pain and psychosocial functioning will be examined in greater detail below.

2.2.5. Treatment Approaches

Reflective of the multiple etiological pathways and psychosocial outcomes, numerous treatment approaches have been suggested and implemented in the care of women with PVD. Vestibulectomy, a surgical treatment involving the removal of the tissue of the vestibule to a depth of about 2 mm, has proven to be the most effective treatment option to date, with success rates ranging from 56 to 94% (Bergeron et al., 2001; Bohm-Starke & Rylander, 2008; Landry, Bergeron, Dupuis, & Desrochers, 2008).

Surgical success rates are much higher for women with secondary, as opposed to primary, PVD (Bohm-Starke & Rylander, 2008; Lambert, Bergeron, Desrosiers, & Lepage, 2012). Although this treatment option boasts high success rates, it is typically viewed as a last resort due to the invasiveness of the procedure (Haefner et al., 2005; McCormack & Spence, 1999). It is also recommended that surgery be performed in addition to psychological counseling, as this combination improves outcomes (Mandal et al., 2010). In support of non-surgical treatment options, a treatment study found that both individual cognitive-behavioural therapy (iCBT) and pelvic floor rehabilitation (PFR) are effective means of managing pain and improving psychosexual correlates of PVD, despite the targeting of different aspects of PVD (Goldfinger, Pukall, Thibault-Gagnon, McLean & Chamberlain, accepted). In addition, a combination of PFR and psychosexual counseling has been shown to lead to decreases in pain and increases in frequency of intercourse (Backman, Widenbrant, Bohm-Starke, & Dahlöf, 2008). Another study found that multidisciplinary treatment (including a medical evaluation and treatment, psychotherapy, physiotherapy, and dietary advice) resulted in improvement of pain symptoms in 93% of their participants (Munday, Buchan, Ravenhill, Wiggs, & Brookes, 2007). Chronic vulvar pain also resolves over time for some women, regardless of whether they engage in treatment (Harlow & Stewart,
2003; Reed et al., 2004), with one study finding that approximately 17% of women with vulvar pain (not necessarily diagnosed as vulvodynia) experienced a resolution of their symptoms after an average duration of 12.5 years of pain (Reed et al., 2012). Increased understanding of the etiological and maintaining factors of this condition will improve efforts at creating individualized treatment options tailored to meet the needs of patients with different subtypes of PVD.

2.2.6. PVD: A Chronic Pain Condition

It is now commonly accepted that PVD is a chronic pain syndrome, a conceptualization first put forth by Dr. Binik’s research lab at McGill University, Montreal, Canada (e.g., Binik et al., 2002). At present, PVD is described as an idiopathic or functional chronic pain, meaning that there is persistent pain in the absence of any identifiable tissue damage (Melzack & Wall, 1996). The discordance between pain and physical findings is a common report in the pain literature. Research has demonstrated that pain can occur in the absence of nociceptive input (e.g., Nikolajsen & Jensen, 2006). The absence of physical pathology should not be taken to imply that the pain is ‘all in the patient’s head’; rather, it is the case that research in chronic pain is in its infancy and we have yet to fully comprehend the mechanisms by which chronic pain may be induced or persist in the absence of visible pathology (Calvino & Grilo, 2006). Neuroimaging studies have provided concrete evidence that chronic pain is a degenerative disease of the brain (Camporesi, Bottalico, & Zamboni, 2011). Prior to examining the neuroimaging pain literature, it is important to discuss the concept of pain more generally.

2.3. What is Pain?

Pain is a complex phenomenon that is studied across a wide number of disciplines, including basic science, psychology, medicine, philosophy, and literature. The first known theories of pain come from the Ancient Greeks; however, Descartes (1596-1650) was the first known individual to view pain as a phenomenon involving signals travelling along nerve fibers to reach the brain. In the 19th and 20th centuries, a number of theories were put forth to explain the sensory experience of pain, including
Specificity Theory (von Frey, 1895), Intensive Theory (Erb, 1874), Peripheral Pattern Theory (Sinclair, 1955; Weddell, 1955), and Gate Control Theory (Melzack & Wall, 1965). Although much of the current understanding builds upon the Gate Control Theory, none of these theories explains pain as we presently understand it with the advantages of modern technology. Indeed, current theories of pain are in flux as new technologies and research strategies are applied to its study to advance our understanding of this complex phenomenon.

Pain is defined by the International Association for the Study of Pain (IASP) as “An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (IASP, 2011). Nociception is the most common cause of pain, and is defined as afferent neural activity transmitting sensory information about a noxious (i.e., painful) stimulus (Treede, 2006). Pain is usually an acute, adaptive mechanism, which induces us to seek help, avoid dangerous situations, or to rest. There are many biological processes involved in the experience of pain, including genetics, hormones, neurotransmitters, and spinal and brain mechanisms. Cortical activity is necessary to the experience of pain (Treede et al., 1999); however, pain includes both peripheral and central mechanisms. The peripheral nervous system consists of nerves that exist outside of the brain and spinal cord, while the central nervous system—the focus of the present study—is made up of the spinal cord and the brain. Peripheral receptors can respond to non-noxious and noxious stimuli. When a noxious stimulus is encountered, pain sensations travel from peripheral nerve endings to the dorsal horn of the spinal cord along both myelinated A-delta fibers, which are quicker at delivering a signal and mediate the initial sharp pain sensation (“first pain”), and C-fibers which are slower and mediate ongoing burning type pain (“second pain”). When the peripheral pain signals arrive at these synaptic regions in the spine, they are thought to be processed through a gate-control mechanism (Melzack & Wall, 1996) and are relayed via the spinal cord to the periaqueductal grey (PAG) and then into the cortical areas of the brain. Simply put, when the gate is open, the pain message is delivered to the brain and the organism experiences pain, and when the gate is closed, the pain is no longer experienced. The gate is opened, or activated, by excitatory
signals. When functioning correctly, the excitatory signals respond to painful, as opposed to non-painful, stimuli. The gate is closed by inhibitory signals, which can result by stimulation of touch fibers in the region of the pain stimulus, or by top-down influences from the brain (e.g., descending modulation), which actively process and modify afferent (i.e., neurons conducting impulses from the periphery to the brain) inputs and can enhance, reduce, or eliminate the perception of pain (Melzack & Wall, 1996). In chronic pain patients, both peripheral and central sensitization can occur. Sensitization refers to the progressive amplification of a response due to repeated stimulation. The processes of peripheral and central sensitization likely result in reorganization of limbic circuitry, which changes the way that pain stimuli are processed in the PFC (Apkarian, Hashmi, & Baliki, 2011).

Traditional views of pain processing were confined to sensory-discriminative processing within the somatosensory cortex; however, it is now clear that pain involves much more than just the sensory component (Coghill, Sang, Misog, & Iadarola, 1999). The experience of pain is made up of three interrelated components: sensory-discriminative, cognitive-evaluative, and affective-motivational. In acute pain, it is generally agreed that the main pathway taken by nociceptive information is through the spinothalamic pathway, carrying the pain message through the brainstem and thalamus into cortical regions (Figure 1; Jones et al., 2003). This pathway was initially assumed to be the primary means by which nociceptive signals were transmitted to the brain, and it was divided into two distinct, but related systems. The lateral system is associated with delta-A fibers and the sensory-discriminative components of pain (i.e., location, spatial & temporal summation, intensity), whereas the medial system is associated with C-fibers and is linked to the affective-motivational and cognitive-evaluative components of the pain experience (i.e., attention & catastrophizing; Jones, Kulkarni & Derbyshire, 2003). These systems are hypothesized to work in parallel in the processing of pain.
Figure 1. Brain areas associated painful stimuli. This figure demonstrates the areas traditionally thought to be part of the medial and lateral pain systems (Jones et al., 2003).

Areas of the brain typically associated with the lateral spinothalamic pathway and the evaluation of the sensory-discriminative aspects of pain are the somatosensory cortices (primary somatosensory cortex, or S1 and secondary somatosensory cortex, or S2), the thalamus, and the IC (Borsook, Sava, & Beccera, 2010). Areas associated with the medial pathway, meaning those associated with the emotional and cognitive processing of pain, are the ACC, IC, PFC, hippocampus, thalamus, basal ganglia, and amygdala (Borsook et al., 2010; Jones et al., 2003; Michael & Burns, 2004). The fairly consistent
activation of these brain regions in healthy participants exposed to acute pain stimuli has led to the concept of the pain matrix (see Figure 1, Jones et al., 2003). The majority of the modern pain literature has been constructed around and interpreted based on the notion of the existence of a pain matrix. A meta-analysis of pain studies using healthy participants supported the presence of activation in many of the regions that make up the pain matrix. According to this meta-analysis, the most common regions of activation across studies in healthy individuals are: the somatosensory cortex (specifically S1 and S2), the thalamus, the IC, the PFC, and the ACC. The ACC is the most commonly activated area across studies, regardless of stimulus modality or measurement techniques; the activation of the ACC is present in 81% of functional magnetic resonance imaging (fMRI) studies (Apkarian et al., 2005). Reviews by other authors also indicate that activations are common in areas such as the basal ganglia, cerebellum, hippocampus, regions of the temporal and parietal cortices, and the nucleus accumbens (Borsook et al., 2010; Schweinhardt & Bushnell, 2010). The pain matrix consists of areas involved in both ascending and descending pain modulation, with psychosocial factors, including expectation, influencing whether inhibitory or facilitatory signals are sent back down the spinal cord. Ascending projections are thought to mainly target the thalamus prior to delivery to cortical structures, and descending projections are mediated through the periaqueductal gray (PAG; Ossipov, Dussor, & Porreca, 2010). Support for the pain matrix comes from findings that these areas of the brain are consistently activated via various types of experimental pain (e.g., thermal, contact, distention), and that perceived intensity of pain correlates highly with the magnitude of neural activation in the areas making up the pain matrix (Iannetti & Mouraux, 2010; Porro, 2003; Rainville, 2002).

While it appears that this model may work relatively well to explain pain, there are many researchers who question both the exclusive use of the spinothalamic tract in the processing of pain signals, as well as the existence of a pain matrix as an exclusive indicator of pain processing (e.g., Apkarian et al., 2001; Iannetti & Mouraux, 2010). Those who question the exclusive use of the spinothalamic tract in processing pain signals report that it is a simplistic model, which does not capture
the entire complex process (e.g., Apkarian et al., 2011; Iannetti & Mouraux, 2010). These research teams argue that there are many other pathways aside from the spinothalamic pathway that can transmit painful information to the brain (Baliki, Geha, Apkarian, & Chialvo, 2008; Schweinhardt et al., 2008), including the spinohypothalamic and the spinoreticular paths (Apkarian et al., 2005).

The existence of the pain matrix has also been called into question based on findings that, although there are specific brain regions that are typically activated with the application of a pain stimulus, pain stimulation rarely results in the activation of the pain matrix alone. Another criticism is that the pain matrix can also be activated by non-painful stimuli (e.g., Lui et al., 2008; Mouraux & Iannetti, 2009). Findings suggest that, while there may be some nociceptive-specific neurons (i.e., neurons that are activated in response to stimuli that have the potential to inflict tissue damage) within the areas of the pain matrix, they are few in comparison to the number of non-specific neurons. For example, the S1 region plays a role in encoding somatosensory information, but does not appear to be directly involved in pain perception (Petrovic, Petersson, Hansson, & Ingvar, 2002). S1 activation was found in 50% or less of pain studies examined in a recent meta-analysis (Apkarian et al., 2005; Peyron, Laurent, & Garcia-Larrea, 2000). Based on these concerns, a series of elegant studies have been conducted to examine the stimuli or conditions that do (or do not) result in activations of the pain matrix. Some researchers now propose a multimodal network, which closely matches the pain matrix, but is dedicated to the processing of salient information, whether painful or otherwise (e.g., Iannetti & Mouraux, 2010; Legrain et al., 2011; Mouraux, Diukova, Lee, Wise, & Iannetti, 2011). This network is hypothesized to play a role in the detection of potential threats to the body. The idea of a multimodal network would account for findings of pain matrix activation in response to non-painful, but salient cues, such as changes in the environment that could be perceived as potential threats.

In support of a saliency network are findings that stimulus novelty enhances the magnitude of nociceptive event related potentials (Legrain et al., 2009). Based on this proposition, the finding that the intensity correlates with neural response can be explained by the fact that more intense stimuli result in
higher saliency. The concept of a saliency detection network is also supported by findings that, when a stimulus is repeated at consistent and short intervals, the magnitude of neural responding decreases, as the stimulus becomes less novel (Iannetti & Mouraux, 2010; Legrain et al., 2011). The extensively researched role of attention in the processing of pain (see below) is also consistent with a saliency detection network, as are the findings regarding pain matrix activations in response to anticipation of pain or painful cues in absence of a physical stimulus, as these appear to provide a nocebo effect (i.e., the expectation of pain may induce an actual increase in pain). Legrain and colleagues (2011) write “the salience detection system would represent a network by which we react to a wasp when viewing the wasp approaching the hand, but even before being stung by it” (p. 121). Despite this conceptual change in thinking about how pain is represented in the brain, and what the pain matrix is actually representing, the areas that make up the pain matrix are consistently activated during acute pain in healthy participants, and the use of this model has been an important, albeit a somewhat simplistic, step in understanding pain in healthy individuals. Chronic pain, on the other hand, has proven to be much more complex than the above models of acute pain, as the brain is constantly reorganizing itself throughout the chronic pain experience (Apkarian et al., 2009).

2.4. Chronic Pain

Chronic pain is pain that is not adaptive. It has historically been defined by arbitrary time points, such as pain lasting for more than three or six months; however, Turk and Okifuji (2002) provided an alternative definition for chronic pain, which is now commonly accepted: pain that extends beyond expected healing time. Approximately 20% of the adult population is estimated to be suffering from chronic pain (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006), and pain accounts for over 80% of all physician visits (Campbell & Edwards, 2007). In Southeastern Ontario, 37% of a sample of over 1000 participants (49% response rate) reported experiencing chronic pain, when this was defined as a minimum of 90 days of pain in the past six months (Tripp, VanDenKerkhof, & McAlister, 2006). The
The financial cost of chronic pain in the United States has been estimated to range from approximately 150 billion dollars per year (Tracey & Bushnell, 2009) to 635 billion dollars per year (Bachmann & Al-Najjar, 2011). In Canada, direct costs of chronic pain (e.g., hospital bills) are estimated at more than 6 billion dollars per year, with indirect costs (e.g., lost time at work) of almost 37 billion dollars per year (National Pain Strategy for Canada, 2010; Phillips & Schopflocher 2008; Schopflocher, Taenzer, & Jovey, 2010). Examples of chronic pain conditions include: fibromyalgia, irritable bowel syndrome, chronic low back pain, headaches, rheumatoid arthritis, and the topic of the current thesis, PVD. Regardless of the specific condition, chronic pain is a multidimensional problem that is subjective in nature. Even with modern technology to assess pain and the use of more multidisciplinary approaches advancing our understanding of this complex subject, we still rely strongly on patient self-report of pain intensity and unpleasantness for the diagnosis of pain (Prkachin, Solomon, & Ross, 2007), rather than a particular diagnostic tool.

Within the chronic pain conditions, there are different classifications of pain type, for example, one of the major distinctions is whether the pain is characterized as nociceptive or neuropathic (or in some cases, mixed). All three types of pain can be acute or chronic in terms of duration; however, nociceptive pain is more likely to be time-limited and neuropathic pain is more likely to become chronic. Nociceptive pain is triggered by activation of peripheral nerve receptors in response to noxious (i.e., painful) stimuli in muscles, bones, organs, and ligaments. Nociceptive pain is experienced as a result of an injury, and the nervous system functions “normally” to relay that pain to and from the brain (IASP, 2012). It is often described as having an “aching” quality. Examples of chronic nociceptive pain conditions include arthritis and mechanical low back pain. Mixed pain conditions can be classified along a spectrum of pain with neuropathic on one end and nociceptive on the other (Bennett et al., 2006). Migraine headaches and low back pain are examples of mixed pain problems. Qualitative descriptors of mixed pain conditions will vary depending upon where the mixed pain lies on the spectrum from nociceptive to neuropathic. The IASP (2012) has also proposed that pain can be classified as definitely, probably, or possibly neuropathic.
Neuropathic pain is a consequence of a lesion or disease in either the peripheral (termed peripheral sensitization) or central (termed central sensitization) somatosensory nervous system (IASP, 2012). This pain is maintained by a number of mechanisms, including excess stimulation of nociceptive pathways and alteration of pain inhibitory pathways. As a result, pain can occur in the absence of a nociceptive stimulus (Woolf & Mannion, 1999). The pain can be spontaneous or evoked by a stimulus. Neuropathic pain is often characterized by a burning or tingling sensation. Examples of chronic neuropathic pain conditions include post-herpetic neuralgia and complex regional pain syndrome (Nicholson, 2006). Neuropathic pain conditions have a wide variety of symptom profiles, with variability across the conditions and even within different patients presenting with the same condition (Attal et al., 2008).

Neuropathic pain can be spontaneous or stimulus-evoked, with stimulus-evoked pain resulting in hyperalgesia and/or allodynia (Ochoa & Yarnitsky, 1993). These characteristics can also be present with nociceptive pain, but are far more common in neuropathic pain conditions (Bennett, 2001). Hyperalgesia is an increased sensitivity to painful stimuli induced either by sensitization of peripheral nociceptors or from sensitization at the spinal or supraspinal level through C-fibre input (e.g., healthy individuals report that a pinprick is painful, but the level of reported pain is higher for individuals with chronic pain). Allodynia is pain evoked by a typically non-painful stimulus when A-beta touch fibers form a pathological connection to nociceptor systems (Woolf & Mannion, 1999; e.g., it is not normally painful to brush a cotton swab over the arm; however, it becomes painful if the arm is sunburned). A meta-analysis examining neural activation of hyperalgesia and allodynia found that allodynia produced different patterns of activation (Lanz, Seifert, & Maihöfner, 2011), supporting the notion that these two pain problems stem from different mechanisms. Based on qualitative descriptors of the pain (e.g., burning and sharp), and evidence of allodynia and hyperalgesia, PVD is suspected by some to contain components of neuropathic pain (e.g., Boardman, Cooper, Blais, & Raker, 2008; Dargie, 2011; Pukall, Binik, Khalifé, Amsel, & Abbott, 2002; Weijmar-Schultz et al., 2005).
Differences between neuropathic and nociceptive pain have been found in a multitude of neuroimaging studies. For example, differences in gray matter density have been found between individuals with neuropathic and non-neuropathic chronic back pain, with larger decreases in gray matter density in the dorsolateral prefrontal cortex (DLPFC) of patients with neuropathic, as opposed to non-neuropathic, chronic back pain (Apkarian et al., 2004). The DLPFC is associated with pain modulation (Lorenz, Minoshima, & Casey, 2003), meaning that for the neuropathic group there may be increased disruption in how pain stimuli are being processed in the brain. The authors suggest that this finding is linked with studies demonstrating that, when compared with non-neuropathic pain patients, neuropathic pain patients have more negative affect, more anxiety, greater somatization, and greater disability (Clarke et al., 2000; Dworkin, 2002). Another study compared individuals with trigeminal neuropathic pain to those with temporomandibular disorders (non-neuropathic). This study found no regional grey matter volume changes in the non-neuropathic group; however, in the neuropathic pain group, there was increased grey matter in the posterior insula, and decreased grey matter throughout other areas of the pain matrix areas, including structures associated with both the lateral and medial pain pathways (Gustin, Peck, Wilcox, Nash, Murray, & Henderson, 2011). Of particular note were the changes in the thalamus associated with trigeminal neuropathy, but not trigeminal neuralgia, suggesting that this area plays a key role in generating and/or maintaining neuropathic pain. Decreased thalamic activity has also been found in neuropathic pain patients compared to healthy control participants (Iadarola et al., 1995). In addition, individuals with neuropathic pain also show increased activity in the pain matrix as compared to those with nociceptive pain, as well as recruitment of cortical areas outside of the pain matrix (Seifert & Maihofner, 2009).

2.5. **Quantitative Sensory Testing**

Quantitative Sensory Testing (QST) is a psychophysical method that encompasses a wide variety of non-invasive tests for the assessment and objective quantification of sensory nerve function (Hansson,
QST has been widely used for assessing individuals with chronic pain conditions in research settings, though it is less commonly employed in clinical contexts (Bergeron, Pukall, & Mailloux, 2005). The particular QST method used in the present study is the method of levels (Yarnitsky & Sprecher, 1994), in which a series of pre-determined levels of stimulation are applied, and the participant reports whether or not the stimulus was perceived and/or painful. The stimuli are applied with increasing levels of intensity, beginning with a non-painful intensity. During application, ratings are collected to investigate different subjective dimensions of pain, such as intensity and unpleasantness of the stimulus. Participants are asked to provide these ratings on a scale, usually ranging from 0 (no pain/no unpleasantness) to either 10 or 100, which represent the worst pain imaginable.

There has been some criticism of the QST method of pain assessment, particularly with chronic pain populations, as the methods assess acute pain within a chronic pain population, rather than actually assessing the chronic pain (Gracely, 1999). Laboratory stimuli differ from naturally occurring pain; for example, there are differences in level of control over the pain and in pain duration, and often studies do not examine a pain location or stimulus type that mimics the clinical condition. Despite these criticisms, numerous studies have demonstrated the relevance of experimental pain (QST) methods in assessing clinical populations (Edwards, Sarlini, Wesselmann, & Fillingim, 2005). Studies have repeatedly demonstrated that individuals with chronic pain have increased experimental pain sensitivity as compared to healthy controls (e.g., Kleinbohl et al., 1999), that their level of experimental pain sensitivity is correlated with their level of clinical pain severity (e.g., Clauw et al., 1999; Edwards et al., 2005), and that they display neural activation in brain regions associated with both the lateral and medial pain pathways (Coghill et al., 1999). In a recent study examining patients with fibromyalgia and chronic fatigue syndrome, pressure pain thresholds and tolerance, but not thermal ones, were correlated with clinical pain as measured by the short form McGill Pain Questionnaire and visual analogue rating scale (Geisser, Gracely, Giesecke, Petzke, Williams, & Clauw, 2007).
A number of research studies have applied QST methodology to examine sensory functioning in women with PVD and have revealed patterns of sensitivity commonly observed in other pain patients. As discussed above, women with PVD have been found to display hyperalgesia (i.e., increased response to painful stimuli) and allodynia (i.e., pain in response to non-painful stimuli). Women with PVD exhibited lower pain thresholds and greater distress to painful stimuli as compared to control women when measured at the vulvar vestibule as well as over the deltoid muscle, suggesting a generalized hypersensitivity to pain (Pukall et al., 2002). This increased sensitivity has been attributed to both peripheral and central nervous system mechanisms given that the increase in sensitivity is present in, but not restricted to, the vestibule. Other studies have supported these findings (Giesecke et al., 2004; Granot et al., 2002; Pukall, Baron, Amsel, Khalifé, & Binik, 2006). Current theory suggests that while local changes in the vulvar vestibule, such as hyperinnervation, may initiate PVD, central nervous system factors may function to maintain the pain (Pukall, Payne, Binik, & Khalifé, 2003). Lowenstein et al. (2004) demonstrated that QST techniques are also capable of discriminating levels of severity in women with PVD; women with more mild cases of PVD did not display the same increases in sensitivity as women with more severe forms of this condition. QST has also been shown to correlate with treatment outcome in chronic pain patients (Edwards, Ness, Weigent, & Fillingim 2003), including those with PVD (Granot, Zimmer, Friedman, Lowenstein, & Yarnitsky, 2004b). In women with PVD, lower experimental pain scores and higher systolic blood pressure were predictive of a reduction in vulvar pain following treatment; higher pre-treatment pain scores correlated with poorer treatment outcomes (Granot et al., 2004b).

2.6. Neuroimaging

Structural and functional neuroimaging studies have revealed many types of brain differences associated with the development of chronic pain, each of which can be affected by sensory-discriminative, cognitive-evaluative, and affective-motivational aspects of pain. According to Seifert and
colleagues (2009), changes include: (1) structural brain alterations in grey matter density and white matter tracts; (2) increased activity in the pain matrix when presented with various types of painful stimuli; (3) additional cortical activity outside the pain matrix when presented with various types of painful stimuli; (4) cortical reorganization; (5) altered neurochemistry; and (6) disruption of the default mode network (DMN), a set of brain regions normally deactivated during task execution; in other words, the DMN is more active at rest (Raichle et al., 2001). Studies have demonstrated that all of these changes may worsen over time (Camporesi et al., 2011), but these brain changes may also be reversible to some extent by effective treatments, including both medication and CBT (e.g., DeLang et al., 2008; Gwilym et al., 2010; Jensen et al., 2012; Lackner et al., 2006; Rodriguez-Raecke et al., 2009; Seminowicz et al., 2011).

2.6.1. Structural Neuroimaging

Structural neuroimaging can examine both grey matter and white matter. Grey matter consists of cell bodies, dendrites, and axon terminals of neurons, while white matter consists of the axons that connect the grey matter regions. Grey matter and white matter volume are examined through voxel-based morphometry (VBM), while the assessment of white matter connectivity has been more recently explored through new technologies such as diffusion tensor imaging (DTI). Grey matter volume (also referred to as density) in the brain is affected by the number and size of brain cells, synaptic density, and dendritic spines (Davis, 2011). Compared with healthy controls, general findings across chronic pain patients with various conditions show decreased grey matter throughout the brain. This decrease in grey matter seems to be related to the chronicity or duration of the pain condition, as well as to increased pain intensity in a variety of chronic pain conditions (Apkarian et al., 2004; Kim et al., 2008; Schmidt-Wilcke et al., 2007), including chronic pelvic pain syndrome (Farmer, Chanda, Parks, Baliki, Apkarian, & Schaeffer, 2011); however, other studies have found no relationship between these variables and grey matter volume (Baliki, Schnitzer, Bauer, & Apkarian, 2011). Structural brain changes are evident in patients with chronic back pain (Apkarian et al., 2004; Schmidt-Wilcke et al., 2006), fibromyalgia (Burgmer, Pogatzki-
Zahn, Gaubitz, Wessoleck, Heuft, & Pfeiderer, 2009; Kuchinad et al., 2007), chronic tension headache and cluster headache (Abstina, Rocca, Colombo, Falini, Comi, & Filippi, 2011; Schmidt-Wilcke et al., 2005), and neuropathic pain (DaSilva et al., 2008).

In a review of structural brain imaging, it was found that the areas of the brain showing changes (the majority of which are decreases) in grey matter varied from condition to condition, but there was overlap in the areas involved in supraspinal nociceptive processing (May, 2007). The primary sites of decreased grey matter in a comparison of 30 studies were the cingulate cortex (19/30 studies), followed by the IC (10/30 studies), the temporal lobe (10/30 studies), the frontal cortex (9/30 studies), the PFC (8/30 studies), and the thalamus/basal ganglia (8/30 studies). These areas are associated with the medial pathway of the pain matrix model, meaning the cognitive and affective processing and modulation of pain (Jones et al., 2003). Other studies found decreased grey matter in the DLPFC, which is an area associated with the ability to modulate pain (Apkarian et al., 2004; Burgmer et al., 2009; Lorenz et al., 2003). Findings support the notion that this volume decrease is reversible, following resolution, or substantial improvement, of the pain condition (e.g. Ruscheweyh et al., 2011).

In contrast to the above-stated findings, Farmer and colleagues (2011) did not find group differences in grey matter between patients with chronic pelvic pain and a control group. Also in contrast to the above-stated findings, a study examining grey matter volume in 14 women with PVD as compared to 14 healthy controls found that PVD subjects had significantly higher, rather than lower, gray matter density in pain modulatory and stress-related areas, such as the hippocampus and basal ganglia (including the globus pallidus, caudate nucleus, and substantia nigra; Schweinhardt et al., 2008). While the majority of studies have found decreases in gray matter density in regions associated with pain modulation, three other studies align with these findings of increased grey matter density: one examining chronic low back pain, one examining fibromyalgia, and one examining cyclic menstrual pain in women with primary dysmenorrhea (Schmidt-Wilcke et al., 2005; 2007; Tu et al., 2010). The latter study found increases in areas involved in pain modulation (e.g., hypothalamus), but decreases in regions associated with affect.
regulation (e.g., insula) and sensory function (e.g., S2). Schweinhardt and colleagues (2008) hypothesize that gray matter alterations may depend on the age of the patient and the duration of disease. They note that there are many psychiatric conditions (e.g., bipolar disorder, obsessive-compulsive disorder, and post-traumatic stress disorder) in which there are increases and decreases in gray matter density. May (2011) suggests that differences between the PVD study and other chronic pain findings in grey matter density may be due to the provoked, rather than spontaneous, nature of PVD. Other authors note that differences amongst studies may also be attributed to methodological and software issues with structural analyses (Apkarian et al., 2011; Gronenschild et al., 2012).

2.6.2. Functional Neuroimaging

Not only are there structural changes evident in patients with various chronic pain conditions, there are also differences in the way they process stimuli, as found through fMRI studies. There are six attributes of functional brain activation that researchers can use to characterize pain, and individuals with chronic pain differ from healthy control participants on all six attributes. The six attributes of activation are: (1) presence or absence; (2) magnitude; (3) location; (4) spatial extent; (5) connectivity; and (6) behavioural correlates\(^1\) (Davis et al., 2006).

Initial fMRI studies found differences in brain activation between control participants and chronic pain patients when these groups were examined during painful and non-painful stimulation; however, later research clarified that differences between pain patients and healthy individuals are usually found because the stimulus used was perceived as painful for the patient group, but not for the control group (Naylor et al., 2012). When the same stimulus level is applied to both groups, resulting in pain for patients, but not for controls (e.g., allodynia is present in the pain group), chronic pain patients show an

\(^1\) Behavioural correlates, which will be examined below, include individual characteristics and/or experimental features, which can be correlated with brain activity (e.g., depression or attention).
increase in neural activity in areas of the pain matrix that is not present in controls. This finding has been demonstrated with fibromyalgia (Giesecke et al., 2004; Gracely et al., 2002), chronic low back pain (Giesecke et al., 2004), and PVD (Pukall et al., 2005). Specifically, individuals with chronic low back pain and those with fibromyalgia showed activation in a variety of pain-related areas, whereas control participants experiencing the same pressure levels had only “faint” activation in the secondary somatosensory cortex. In contrast, in studies where pain intensity ratings were matched between the groups (meaning they received different pressures or temperatures to correspond with a particular pain rating), there are subtle, if any, group differences between patients and healthy individuals across a variety of chronic pain conditions, including chronic low back pain (Baliki et al., 2010) and fibromyalgia (Cook et al., 2004; Giesecke et al., 2004; Gracely et al., 2002). In conclusion, it appears that individuals with chronic pain have lower pain thresholds compared with controls, and these result in increased pain processing; however, when stimuli are matched so that the intensity rating is the same between groups, the brain processes these stimuli of matched pain intensity in a similar manner.

Numerous studies have demonstrated altered resting-state activity in individuals with chronic pain. Resting state can be defined as “the state of the brain of a subject awake and not engaged in any demanding sensory, motor, or intellectual activity” (Apkarian et al., 2009, p. 95). When functional connectivity of brain areas in patients with chronic neuropathic pain is examined during resting state, the parieto-fronto-cingulate network, which controls attention to external stimuli, has been found to be impaired (Cauda et al., 2010). Specifically, the researchers found widespread reduction in the connectivity between dorsal and ventral attention networks, and the dorsal ACC. In patients with fibromyalgia, as compared with healthy controls, there was an imbalance in the functional connectivity in the pain network. Findings indicated increased connectivity in areas involved in pain processing and decreased connectivity in areas involved in pain inhibition (Cifre et al., 2012). Other researchers have also found that, as compared to control participants, individuals with fibromyalgia have greater connectivity in
the DMN, and between the DMN and the insula (Napadow et al., 2010). Individuals with low back pain have reduced deactivations (e.g., increased activation) in the DMN (Baliki et al., 2008).

2.7. From Acute to Chronic Pain: The Role of Psychology

2.7.1. Chronification of Pain

Apkarian and colleagues (2009) put forth a general model of chronic pain that expands upon the above-described model of acute pain. They propose that there is a temporal transition from a more sensory-dominant experience of acute pain, to a more affective-dominant experience with chronic pain. During this temporal transition, the salience of pain (i.e., the attention) shifts from external threat to an internal disease state in which threat assessment and memory/learning of pain directly modulate the extent to which each pathway is activated. Consistent with this hypothesis, there is now a general consensus that chronic pain involves alteration in the brain systems that regulate attention, emotion, motivation, and memory, in addition to changes in the sensory-discriminative aspects associated with the somatosensory cortex (Borsook et al., 2010). Emotional reactions interact with pain cognitions to amplify the sensory pain experience.

Research on psychosocial effects of chronic pain began in the clinical research field and has now also been supported by neuroimaging findings, which demonstrate that psychosocial factors can modulate activation of brain areas associated with pain. It has been demonstrated by numerous studies that differences in brain activation between pain types, various studies, and participants is due in part to the important role of psychological and social context² in the modulation of pain intensity, especially in chronic pain populations (e.g., Campbell & Edwards, 2009; Edwards, 2005; Heyneman, Fremouw, Gano, Kirkland, & Heiden, 1990; Keefe, Rumble, Scipio, Giordana, & Perri, 2004; Masheb, Nahs, Brondolo, & ²Hereby referred to collectively as “psychosocial.”
Kerns, 2000; Schweinhardt et al., 2008; Turk & Okifuji, 2002). Psychosocial factors can function both to increase (e.g., catastrophizing) and decrease (e.g., self-efficacy) adjustment to pain and pain perception (Keefe et al., 2004). Despite numerous studies examining the psychosocial components of pain, it is still necessary to focus on psychosocial variables, as there is much more to be learned and understood about their role in the processing and maintenance of pain (Rapps, van Oudenhove, Enck, & Aziz, 2008).

Findings from numerous studies suggest that the most reliable psychosocial predictors of hyperalgesia are anxiety, fear of pain, and catastrophizing (Sullivan, Bishop, & Pivik, 1995; Sullivan et al., 2001), all of which function to increase attention to the pain stimulus (e.g., hypervigilance). In addition, higher pain-related fear and hypervigilance, catastrophizing, and avoidance of pain-related activities are associated with reduced treatment efficacy (Leeuw et al., 2007). One means by which the relationships among these variables can be explained is through the use of the cognitive-behavioural fear-avoidance model (Figure 2; Lethem et al., 1983; Vlaeyen & Linton, 2000).

![Figure 2](image)

*Figure 2.* The fear-avoidance model of pain, which accounts for the role of pain related catastrophizing and fear in the chronification of pain (Vlaeyen & Linton, 2000).
This model suggests that catastrophizing, avoidance, and fear play a primary role in the transition to, and maintenance of, chronic pain (Buer & Linton, 2002; Asmundson, Norton, & Norton, 1999; Vlaeyen & Linton, 2000). Anxiety sensitivity, which is the trait-like tendency to be fearful of anxiety-related sensations based on the belief of harm (Reiss & McNally, 1985), is also a crucial variable in this cycle, as it likely plays a role in explaining individual differences in fear of pain (Norton & Asmundson, 2004) and consequent avoidance of potentially painful situations (Vlaeyen & Linton, 2000). Findings suggest that, even when controlling for the effects of pain severity, individuals with high anxiety sensitivity have higher pain-related anxiety and fear, greater cognitive disruption, and greater use of analgesic medication (Asmundson & Norton, 1995; Asmundson & Taylor, 1996). It is thought to amplify pain-related fear and anxiety (Reiss & McNally, 1985; Reiss, 1991), and path analysis and mediation models have suggested that it exacerbates beliefs that promote fear-avoidance and negative interpretation of body sensations (Asmundson & Taylor, 1996; Keogh, Hamid, Hamid, & Ellery, 2004). Scores on a measure of anxiety sensitivity (Anxiety Sensitivity Index; ASI) in healthy individuals predicted activation of the medial PFC in a region associated with self-focus (Ochsner et al., 2006).

The relationship between anxiety sensitivity and fear of pain is hypothesized to be explained by attention (Reiss, Peterson, Gursky, & McNally, 1986). For example, chronic pain patients who were low on anxiety sensitivity shifted their attention away from the pain-related stimuli presented in the experiment, whereas those high on anxiety sensitivity did not (Asmundson, Kuperos, & Norton, 1997). Individuals who catastrophize and fear pain symptoms have a tendency to be hypervigilant to pain, in other words, to focus attention on the pain experience excessively (Crombez, Eccleston, Baeyens, van Houdenhove, & van den Broeck, 1999; Crombez, VanDamme, & Eccleston, 2005; Sullivan et al., 1995; Van Damme et al., 2004). This increased focus, or attention, to pain results in pain amplification (Vlaeyen & Linton, 2000). Such amplification of pain may occur by altering the central threshold of excitability over time and eventually increasing one’s sensitivity to pain (Melzack, 1999). This increased sensitivity might occur by activation of a brain network that overlaps with the pain matrix and is thought to be
associated with stimulus novelty and salience (Legrain et al., 2011) as well as areas associated with self-focus and self-monitoring (Ochsner et al., 2006). Avoidance of pain promotes this cycle by not enabling the individual to falsify their negative beliefs about pain or the self in relation to pain, thus increasing fear and anxiety over time, and entrenching the learned conditioned response to pain (Apkarian et al., 2011). In other words, not only is chronic pain a combination of continuous exposure to pain resulting in a cognitive bias toward pain, but due to avoidance of potentially painful activities, there are reduced opportunities to be exposed to situations in which the individual is able to unlearn the pain. Research on women with PVD has demonstrated that they often avoid pain-provoking activity (for example, intercourse; e.g., White & Jantos, 1998) and that they have a fear of pain (Payne et al., 2005), which may function to entrench learned schemas about pain.

2.7.2. Affective Aspects of Pain

2.7.2.1. Anxiety

It is common for individuals in pain to feel anxious, particularly when the pain is unexplained, as it is in many chronic pain conditions, including PVD. As noted above, anxiety and fear of experiencing or exacerbating the pain may lead to avoidance of activity in an effort to protect oneself from further harm, which in turn can lead to greater disability and poorer psychosocial functioning (Boersma & Linton, 2006). Anxiety and fear of pain are related, but separate, constructs. Anxiety can be defined as a generalized, non-specific distress, whereas fear is experienced in response to an identifiable threat (Davis, 1998; Payne et al., 2005). Anxiety has been associated with pain perception in a variety of chronic pain studies (Keefe et al., 2004), including those examining PVD (e.g., Jantos, 2008). For example, women with PVD report significantly higher state (Granot et al., 2002; Nylanderlundqvist & Bergdahl, 2003; Payne et al., 2005) and trait anxiety than control women (Nunns & Mandal, 1997; Payne et al., 2005). Higher levels of anxiety toward intercourse were associated with earlier onset and longer symptom duration (Brotto, Basson, & Gehring, 2003). Experimentally, researchers have linked anxiety and pain,
finding that pain thresholds in both pain-free control populations and chronic pain populations, including women with PVD, are mediated by anxiety (Arntz, Dreessen, & De Jong, 1994; Granot et al., 2002; McCracken, 1997). For example, in women with PVD, state and trait anxiety predicted an attentional bias toward pain words on the emotional Stroop task (Payne et al., 2005). Anxiety scores in IBS patients correlated with pain activations in the anterior mid-cingulate cortex (MCC) and the perigenual ACC, areas associated with cognitive and affective pain processing, suggesting the role of altered psychosocial functioning in this disorder (Elsenbruch et al., 2010). Others have found increased activation in the entorhinal cortex of the hippocampal formation during anxiety-modulated pain in healthy participants (Ploghaus et al., 2001). This region is associated with pain processing (e.g., Hebben, Corking, Eichenbaum, & Shedlack, 1985) and modulation (Fiore et al., 1999), as well as memory (Suh, Rivest, Nakashiba, Tominaga, & Tonegowa, 2011), which is consistent with the role of learning and memory in chronic pain. In addition, functional connectivity between the insula and brainstem has been found to depend on trait anxiety, suggesting the influence of this variable on descending neural mechanisms of pain. Individuals who are higher in anxiety show weaker connectivity, suggesting that they have disrupted descending pain modulation (Ploner et al., 2010). The literature on the relationship between anxiety and brain activity during pain is equivocal, as others have found that trait anxiety was not significantly correlated with BOLD activation in healthy individuals (Ochsner et al., 2006). No study to date has examined the neural correlates of anxiety in women with PVD.

2.7.2.2. Fear of Pain and Pain Anxiety

Fear of pain has been demonstrated to be a better predictor of disability than pain duration or severity (e.g., Turk, Robinson, & Burwinkle, 2004, Crombez et al., 1999). Pain-related anxiety and fear of pain are associated with poorer coping skills (McCracken, Gross, Sorg, & Edmands, 1993) and reduction in pain-related anxiety is associated with improvement in pain symptoms (McCracken & Gross, 1998). Higher levels of fear of pain, as measured by the Fear of Pain Questionnaire (FPQ), have been associated
with brain activation in the ventral lateral frontal region and the anterior and posterior cingulate regions. These areas are associated with response regulation, pain amplification, and the monitoring and evaluation of affective responses (Ochsner et al., 2006; Schweinhardt et al., 2008). When fear and negative emotions are induced in a laboratory setting, individuals demonstrate higher activation in the ACC (Malin & McGaugh, 2006), IC (Phillips et al, 2003), amygdala, and hippocampus (Apkarian et al., 2009). The amygdala has also been associated with Pavlovian fear conditioning (Kennedy et al., 2012). A study that induced pain-relevant anxiety in healthy control participants also found associations with this variable in the entorhinal cortex of the hippocampal formation (Ploghaus et al., 2001).

The tendency to fear pain may mediate individual differences in pain intensity (Eccleston, 1995), attention to pain (Asmundson et al., 1997), and anticipation of pain (Eccleston et al., 2001). Neural activation associated with fear of pain may be reflected in studies examining anticipation of pain, rather than the pain stimulus itself, since fear is an emotion that precedes the painful event. Studies have found that pain anticipation is accompanied by fear, and results in activation of the ACC (Hsieh, Stone-Elander, & Ingvar, 1999), PFC, insula (Porro et al., 2002), and hippocampus (Ploghaus et al., 2001), all of which are associated with emotional and cognitive processing of pain. More recently, pain anticipation has also been associated with activation of the S1, a finding that might suggest a functional heterogeneity in this region, with responses to both sensory and attentional components of pain processing (Worthen et al., 2011). Individuals who score high on pain-related fear and anxiety report high levels of attention to pain sensations (Crombez, Vlaeyen, Heuts, & Lysens, 1999; McCracken, 1997) and show a greater attentional bias toward pain-related information than those who are low on fear of pain (Keogh, Ellery, Hunty, & Hannet, 2001). As noted above in the fear-avoidance model of pain, when individuals are fearful of experiencing further pain, or of exacerbating their pain, they may become hypervigilant to painful experiences, rendering even mildly painful experiences more noticeable, as well as increasing muscle tension, thus potentially exacerbating pain (Vlayen & Linton, 2000). For women with PVD, fear of pain is predictive of self-report measures of hypervigilance during intercourse (Payne et al., 2005).
As evidenced above, pain is modulated by emotional regulation, including anxiety; however, emotional regulation also involves cognitive factors, both of which are important in the chronification of pain (Wiech, Ploner, & Tracey, 2008).

2.7.3. Cognitive Aspects of Pain

2.7.3.1. Attention

The sensation of pain is critical for survival and thus immediate and dominating attention to pain is a necessary strategy in the short term (Asmundson et al., 1999). The problem with attentional focus on pain occurs when the pain becomes chronic. The role of attention in the processing of pain has been examined in both healthy control participants and in individuals with various chronic pain conditions, and attention has been found to be an important factor in modifying pain perception (Peyron et al., 1999; Rapps et al., 2008; Villemure & Bushnell, 2002). More specifically, activation of the S1, S2, ACC, IC (Villemure & Bushnell, 2002), and thalamus (Valet et al., 2004) has been associated with attention-related pain modulation. As discussed above, researchers suggest that stimulus saliency, regardless of sensory modality, activates a cortical network that closely resembles the pain matrix (Downar et al., 2003). Studies have found that novel nociceptive stimuli involuntarily catch the attention of the participant, resulting in increased brain activation (Legrain et al., 2009), a finding that aligns with other sensory modalities (e.g., visual or auditory stimuli; Friedman et al., 2001). This attention-specific network (which overlaps with cognitive-affective regions of the proposed pain matrix) includes the DLPFC, anterior and posterior cingulate cortices, posterior parietal cortex, and medial frontal cortex (Seminowicz & Davis, 2007). Legrain and colleagues (2011) believe that brain responses to pain reflect, at least to some degree, the processing of salient sensory information, which receives more attention than non-salient information.

Attention to pain is a significant predictor of distress, disability, and daily functioning, independent of pain intensity levels (McCracken, 1997). In healthy individuals, attention can be directed away from an acute pain stimulus through the use of an interference Stroop test, resulting in decreased
pain ratings and decreased cortical activation in the pain matrix (Bantik, Wise, Ploghaus, Clare, Smith, & Tracey 2002). However, for individuals with chronic pain, directing attention away from the pain source can prove to be a difficult task, as they have biased information processing that results in selective attention to stimuli that are consistent with their pain schema (in this case, chronic pain; Clark & Beck, 2010). Individuals with IBS, for example, show greater recall for gastrointestinal (GI) sensation words as opposed to asthma words or neutral words (Gibbs-Gallagher et al., 2001) as well as an attentional bias resulting in poorer performance on an emotional Stroop test (Chapman & Martin, 2011). A study examining selective attention in individuals with IBS concluded that when attention is divided between two sensory modalities, information related to pain in these patients was preferentially processed as compared to information related to the visual sensory modality (Gregory et al., 2003). This finding indicates that, in individuals with chronic pain, there is an automatic tendency to focus on the pain area above all else. Another study examining cortical mapping of pain in patients with GI disorders found augmentation of brain activity in the ACC, an area of the brain found in the medial pain pathway that is associated with attentional processes (Bernstein, Frankenstein, Rawsthorne, Pitz, Summers, & McIntyre, 2004). Whether pain focus (e.g., hypervigilance and attention to pain) precedes or results from the pain is not yet known; however, one study partially supports the idea that there are pain-related implicit memory structures in the brain within chronic pain populations: Flor and colleagues (1997) showed that pain patients had enhanced left hemisphere N100 and N200 event-related potentials (ERPs; indicative of preconscious attention) for pain-related versus neutral or body-related words.

As implied above, one way in which to study the role of attention through experimental procedures is to present participants with stimuli that either draw attention towards, or away from, the pain. A number of studies have examined the effects of painful words on healthy participants, all of which have demonstrated nocebo effects of painful words. Richter and colleagues (2010) conducted an elegant experiment aimed at identifying whether the effect of pain words was due to the pain or to more general negative valence. They also investigated whether brain activation to pain words was affected by attention
to the word versus distraction. They concluded that there is an increase in activation in the left inferior parietal gyrus, the precuneus, and the left DLPFC during painful words as compared with unpleasant, pleasant, and neutral words. These areas are reportedly related to the cognitive/attentional dimension of the pain (Peyron et al., 2000). The researchers also found that pain-related words activated regions of the pain matrix to a greater extent when the participants explicitly attended to the words (Richter et al., 2010). Other researchers have also found that reading painful words is not enough to activate pain areas in the brain—paying attention to those words is required (Gu & Han, 2007).

Chronic pain patients with various syndromes also demonstrated enhanced physiological reactivity to painful words (Jamner & Turskey, 1987; Salamy et al., 1983). Individuals with chronic upper back pain show enhanced skin conductance and evoked response potentials (ERPs) to pain-related words as compared with controls (Flor et al., 1997). When doing a task in which painful activities related to low back pain were visualized, a group of low back pain patients showed enhanced activation, as compared with controls, of brain areas related to pain (Shimo et al., 2011). Individuals with chronic phantom limb pain also showed enhanced processing of pain-related visual stimuli as compared with those who did not develop phantom limb pain (Larbig et al., 1996). Although there have not been any imaging studies to date examining the role of attention in women with PVD, these women report hypervigilance for pain during intercourse and exhibit a selective attentional bias toward pain stimuli presented on an emotional Stroop Task, which can function to increase the stimulus salience and perceived pain intensity (Payne et al., 2005).

Numerous studies have provided empirical support for the relationship between attention and pain catastrophizing, which functions as an inability to suppress pain-related cognitions and behaviours (Quartana, Campbell, & Edwards, 2009). A study on patients with low back pain concluded, through structural equation modeling, that pain vigilance is very likely dependent upon catastrophizing and pain-related fear (Groubert, Crombez, & Van Damme, 2004). Higher levels of pain catastrophizing have also been associated with decreased pain threshold and tolerance between a first and second cold-pressor pain
task when participants were asked to read a list of pain-affect words between the two tests, thus drawing their attention to the pain stimulus. Conversely, decreased pain tolerance and threshold were not observed in tasks where participants read pain-sensory or control words that did not draw their attention to the pain stimulus (Michael & Burns, 2004). Individuals who engage in catastrophic thinking about pain report greater difficulty suppressing pain-related thoughts (Sullivan, Bishop, & Pivik, 1995).

2.7.3.2. Catastrophizing

Pain catastrophizing, the tendency to magnify and ruminate about pain, in addition to adopting a helpless stance, is characterized by an exaggerated negative interpretation of pain (France, France, al’Absi, Ring, & McIntyre, 2002; Rosentiel & Keefe, 1983, Sullivan et al., 2001) and a relative inability to inhibit pain-related thoughts (Quartana et al., 2009). According to Burgmer and colleagues (2011), it can be treated as a continuous, normally distributed variable in a healthy population, with predictive value for developing pain conditions. As compared with controls groups, higher levels of pain catastrophizing have been found among many different chronic pain syndromes such as fibromyalgia (Gracely et al., 2004; van Wilgen et al., 2008), low back pain (Flor, Behle, & Birbaumer 1993), and PVD (Sutton, 2007). Studies have demonstrated that women with PVD catastrophize more in response to their vulvar pain than to their most distressing, regularly experienced non-vulvar pain condition, and they catastrophize more about both their vulvar pain and their most distressing non-vulvar pain condition compared with control women (Pukall et al., 2002, 2005a). In addition, another study showed that catastrophizing contributed unique variance to intercourse pain in women with PVD, above and beyond the effects of fear of pain, hypervigilance, and self-efficacy. Taken together, these variables accounted for 15% of the variance in pain intensity during intercourse (Desrochers, Bergeron, Khalifé, Dupuis, & Jodoin, 2009).

From a psychosocial perspective, catastrophizing has a negative effect on one’s social environment and ability to cope, and it is correlated with pain-related disability and pain behaviours (Gracely et al., 2004; Sullivan et al., 2001). It was found to be the single most important predictor of
quality of life in a heterogeneous sample of pain patients (Lamé et al., 2005). Catastrophizing is positively correlated with pain perception in both healthy individuals (e.g., Sullivan et al., 2001), and those with chronic pain (e.g., Sullivan et al., 1998). Higher levels of pre-surgical pain catastrophizing predicts pain levels post-surgically in healthy individuals (e.g., Edwards, Fillingim, Maixner, Sigurdsson, & Haythornthwaite, 2004; Riddle, Wade, Jiranek, & Kong, 2010), with one study finding that catastrophizing accounted for 47% of the variance in the prediction of the development of chronic pain from an acute pain experience (Burton et al., 1995). Level of catastrophizing can also be predictive of pain progression in chronic pain patients (e.g., Velly et al., 2011), with higher levels being predictive of higher pain intensity, greater disability, and more psychological distress (Severeinjns, Vlaeyen, van den Hout, & Weber, 2001).

Higher levels of catastrophizing are linked with greater pain reports and lower pain threshold and tolerance in experimental paradigms (Edwards et al., 2004; Edwards, 2005; Flor, Behle, & Birbaumer, 1993; France et al., 2002; Granot & Lavee, 2005; Severeijns et al., 2001). It is thought that, in both chronic pain patients and healthy populations, catastrophizing increases pain reports due to an exaggerated attention bias to both sensory and affective pain information (Eccelston & Crombez, 1999). In both healthy controls and chronic pain patients, catastrophic thinking impairs the ability to be distracted from pain (Crombez, Eccleston, Baeyens, & Eelen, 1998; Heyneman et al., 1990). In zero-order correlations, catastrophizing has been found to account for 7 to 31% of the variance in pain ratings (Sullivan et al., 2001); however, a later review paper reported that it has accounted for minimal variance in other studies (Quartana et al., 2009). Although there has been a great deal of research addressing the relationship between catastrophizing and pain, the mechanisms by which catastrophizing maintains or worsens chronic pain are still not completely understood (Quartana, Burns, & Lofland, 2007; Leung, 2012), and it remains a controversial construct in the literature. It is hypothesized that catastrophizing affects top-down pain processing (Wiech et al., 2008), as opposed to spinal or peripheral pain processing. This hypothesis is supported by evidence that catastrophizing does not modify spinally-mediated
withdrawal reflexes (France et al., 2002). It is also supported by evidence of negative associations between catastrophizing and a descending pain mechanism termed diffuse noxious inhibitory control (DNIC), such that increased catastrophizing is associated with less effective pain inhibition through DNIC mechanisms (Edwards & Fillingim, 2001; Goodin et al., 2008; Weissman-Fogel, Sprecher, & Pud, 2008). There is also a positive relationship between catastrophizing and temporal summation, which is the increase in perceived pain intensity with the application of multiple noxious stimuli delivered in close temporal sequence (Edwards, Bingham, Bathon, & Haythornthwaite, 2006; George, Dannecker, & Robinson, 2006). Findings of activation in the PFC are also consistent with this hypothesis. The association between catastrophizing and pain has been hypothesized by some researchers to be affected by anticipation, increased emotional responding, and increased attention to the pain stimulus (Gracely et al., 2004; Sullivan et al., 2001). Although many hypothesize that pain schemas developed in high catastrophizers may lead these individuals to a preferential processing of pain-related or ambiguous potential pain information (e.g., Cioffi & Holloway, 1993), others believe that whether catastrophizing is associated with increased attention to pain above and beyond variables of fear of pain and pain anxiety remains to be studied (George et al., 2006; Quartana et al., 2009).

A study on individuals with fibromyalgia concluded that attention is one of the means through which catastrophizing can increase pain perception (Gracely et al., 2004), with findings of increased brain activation in areas related to attention such as the dorsal ACC and the DLPFC. By engaging in cognitive activity that amplifies pain signals, such as increased attention to pain, central neural mechanisms may become more sensitized, thus yielding a chronic state of hyperalgesia (Sullivan et al., 2001). For individuals with chronic musculoskeletal pain, high catastrophizers appeared to be more susceptible than low catastrophizers to processing information that is consistent with their pain schemas (Michael & Burns, 2004). Greater catastrophizing is also associated with slower attentional disengagement from pain-related cues (France et al., 2002). When controlling for depression, a construct thought by some to overlap substantially with catastrophizing (noted in Sullivan et al., 2001), high levels of catastrophizing in
individuals with fibromyalgia resulted in greater increases of activation in areas such as the S2 and thalamus, as well as unique activation in the contralateral ACC that is not found in those patients with low levels of catastrophizing (Gracely et al., 2004). In women with PVD, pain catastrophizing is positively correlated with grey matter density in the parahippocampus/hippocampus and the substantia nigra, an area associated with motor planning and learning. Hippocampal dysfunction has also been demonstrated in patients with fibromyalgia (Emad, Ragab, Zeinhom, El-Khouly, Abou-Zeid, & Rasker, 2008), although the researchers in this study did not examine the role of catastrophizing, other studies have demonstrated that individuals with fibromyalgia score higher on catastrophizing than healthy controls (Edwards et al., 2006). Another study examined catastrophizing in healthy participants, with findings that, during a mild pain stimulus, participants who had higher levels of pain catastrophizing displayed increases in brain regions associated with the affective, attention, and motor areas, including the DLPFC, the insula, and the rostral ACC (Seminowicz & Davis, 2006). During more intense levels of pain, catastrophizing is negatively correlated with the prefrontal cortical regions associated with top-down pain modulation, suggesting that catastrophizing impedes one’s ability to disengage from or suppress the more intense perceptions of pain (Seminowicz & Davis, 2006). Greater helplessness, an aspect of catastrophizing, or feeling a lack of control over the noxious stimuli applied in an experimental setting, resulted in greater activation of the IC and the perigenual ACC (Salomons et al., 2007). In a depressed sample, helplessness and rumination—components of catastrophizing—were associated with higher activation in the amygdala during application of a pain stimulus (Strigo et al., 2008). Such findings are useful in a chronic pain model explain the connection among the roles of attention, catastrophizing, and pain intensity.

2.8. **Current Study**

There remains a great deal to understand regarding the etiology and maintaining factors of PVD in order to provide better informed treatment options. First, despite much research on psychosocial functioning in women with PVD, there is still a need to examine the variables associated with the fear-
avoidance model of pain in this population. Although anxiety and catastrophizing have been studied by many research teams, and found to be heightened in women with PVD, the neural correlates of these variables in women with PVD remains to be thoroughly investigated. Both anxiety and catastrophizing are associated with increased hypervigilance to pain; however, although pain related hypervigilance refers to a heightened state of attention to potentially painful stimuli, the experimental manipulation of attention to pain has not been thoroughly examined in women with PVD. Second, despite evidence suggesting PVD consists of subtypes based on temporal onset (primary and secondary), women with this condition continue to be treated as a homogenous group; further studies that continue to examine these potential subgroups will assist in the future diagnosis and treatment of PVD.

The purpose of the current study was twofold: (1) to examine neural correlates of variables associated with the fear-avoidance model of pain (attention, catastrophizing, and anxiety); and (2) to examine differences in neural activation between women with primary and secondary PVD. Specifically, the following research questions were addressed: (1) Does attention play a greater role in pain processing for women with PVD as compared with control women when attention is measured through a paradigm pairing painful and non painful words with painful and non-painful pressures? (2) Do catastrophizing and anxiety differ between groups in their correlations with areas of neural activation during pain? (3) Do women with primary and secondary PVD differ in psychosocial functioning and neural activation during painful stimulation?
Chapter 3. Research Questions and Hypotheses

Prior to examining specific research questions, analyses were conducted with the aim of confirming the group differences in psychophysical and sexual functioning that are reported in the PVD literature. Based on the existing literature, it was hypothesized that group differences between women with PVD and healthy controls would exist on pain variables (e.g., gynecological pain ratings, intercourse pain ratings), psychophysical variables (e.g., pressure pain thresholds, moderate pressure pain thresholds), and sexual variables (e.g., sexual self-efficacy, sexual functioning).

This cross-sectional, multipart study consisted of three major components, each adding a unique contribution to the literature. The first study used a factorial design to examine neural activations associated with painful and non-painful pressures, as well as with painful versus non-painful words in control women and women with PVD. The presentation of words immediately prior to the application of a pressure stimulus was conducted with the goal of examining the role of attention in pain processing. Study two examined psychosocial variables associated with anxiety and catastrophizing, as well as the correlations among anxiety, catastrophizing, and neural activation during the application of a pressure pain stimulus. Correlations were examined for women with PVD and control women, as well as between individuals scoring high and low on the psychosocial measures regardless of pain group status. Study three examined psychosocial variables and neural activations during the pressure pain between women with primary and secondary PVD.

3.1. Study 1

As attention plays a key role in the fear-avoidance cycle of pain (Vlaeyen & Linton, 2000), the main goal for this part of the study was to investigate whether attention influences pain perception in women with PVD and healthy control women. Attention was examined by presenting either a painful word descriptive of PVD (e.g., burning) or a neutral word one second prior to the application of a pressure stimulus. The role of attention was examined by using a 2 x 3 factorial design with stimuli
consisting of words (painful, neutral) and pressures (painful, touch, no pressure; Appendix A). Main
effects and interactions of the factor design were assessed.

(1) It was hypothesized that drawing attention to pain would result in a higher magnitude of
neural activations in the pain matrix for women with PVD as compared with control women.
As such, women with PVD would display higher activations than control women during the
conditions in which they were presented with a painful word and a pressure stimulus. For
specific hypotheses associated with the main effects and interactions, see Appendix B.

3.2. Study 2

The first aim of the study was to examine group differences in anxiety and catastrophizing
variables. The second aim was to examine whether correlations between neural activation during a painful
stimulus and scores on trait-anxiety, pain-related anxiety, and catastrophizing measures. The third aim of
this study was to examine whether there were differences in neural activation for high anxiety and high
catastrophizing, as compared with low anxiety and low catastrophizing, regardless of PVD/control group
membership. This hypothesis was examined by dividing the whole sample into high and low responders
based on cut-off scores denoted in research using these measures with clinical populations. These
psychosocial/cognitive variables were chosen because they play a key role in the maintenance of chronic
pain (Sullivan et al., 1995; Sullivan et al., 2001), and thus, they may contribute to changes in the way pain
is processed.

(1) It was hypothesized that women with PVD would display higher levels anxiety and
catastrophizing as compared with control women. This hypothesis is consistent with
numerous findings in the literature (e.g. Payne et al., 2005; Sutton et al., 2009).

(2) It was hypothesized that, during the application of a pain stimulus, anxiety and
catastrophizing scores from the psychosocial measures would be correlated with areas of the
pain matrix involved in affective and cognitive processing. Based on findings in the literature,
positive correlations were expected in attention/affective associated areas such as the ACC, insula, and motor areas (e.g., SMA). Negative correlations were expected in the pre-frontal cortex, as was previously found during moderate pain stimuli in healthy individuals, likely reflecting problems with pain modulation (Seminowicz & Davis, 2006).

(3) It was hypothesized that, in affective brain regions, women with PVD would have a greater number of negative neural correlations in areas of the pre-frontal cortex than the control group, as they have more difficulty disengaging from pain (France et al., 2002).

(4) It was hypothesized that, regardless of group membership, during a painful pressure stimulation, higher psychosocial dysfunction would result in greater activation regions associated with affective processing of pain, and greater deactivation in areas of the pre-frontal cortex associated with pain modulation (e.g., the DLPFC).

3.3. Study 3

The main goal of this study was to examine group differences in women with primary and secondary PVD. These groups were examined for differences in psychophysical functioning, psychosocial functioning, and neural activation during a pain stimulus.

(1) Based on previous findings in the literature (e.g., Goetsch, 1991; Granot et al., 2004a; Sutton et al., 2009), it was hypothesized that women with primary PVD would have lower pain thresholds and poorer psychosocial functioning than women with secondary PVD.

(2) Based on findings that women with primary PVD have greater dysfunction than those with secondary PVD, it was hypothesized that women with primary PVD would display greater magnitude of neural activation in the pain matrix for pain and touch stimuli than women with secondary PVD.
Chapter 4. Methods

4.1. Participants

Participants were recruited from the Sexual Health Research Lab (SHRL) participant database and from flyers posted at doctor’s offices, around campus, and throughout the Kingston community (Appendix C). Interested participants were asked to contact the SHRL at Queen’s University in order to receive more detailed information regarding the study procedures. If, after hearing more about the study, the participants were still interested, they were screened for eligibility using a brief (approximately 20 minute) telephone screening interview (Appendix D). One hundred and eleven women expressed interest in the study (64 PVD and 47 controls) and were screened via telephone for participation. Of these women, 61 (33 PVD and 28 controls) were eligible following the telephone screening interview, and they were invited to attend a gynecological examination to confirm their eligibility (see below). Thirty-seven women (19 PVD and 18 controls) were eligible following the gynecological examination, and were invited to attend the experimental session involving an interview, questionnaires, sensory testing, and fMRI testing. A total of 15 women in each group completed the non-fMRI portions of the study, and 14 per group completed the fMRI portion of the study. Reasons for ineligibility are listed in Table 1. The interview/questionnaire session was conducted prior to the sensory/fMRI session and was approximately one hour in length. All of the sensory and fMRI testing was completed over the course of the same session, which was approximately 2-3 hours in length. To compensate for their time, participants received CAN $100.00 upon completion of the study. For those deemed not eligible after the gynecological examination, or who chose to withdraw from the study, a partial sum of this amount was paid for the time invested. Upon completion or withdrawal, a debriefing form was provided (Appendix E). All participants gave written and verbal informed consent. The experimental protocol was approved by the Queen’s University and Kingston General Hospital Research Ethics Boards.
### Table 1

*Reasons for exclusion of participants at various stages of the study*

<table>
<thead>
<tr>
<th>Reason for Exclusion</th>
<th>Control group</th>
<th>PVD group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tel</td>
<td>Gyne</td>
</tr>
<tr>
<td>No previous gynecological exam</td>
<td>1</td>
<td>n/a</td>
</tr>
<tr>
<td>On centrally acting medication</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Other medical diagnosis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ineligible based on fMRI safety</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Did not meet pain criteria</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Inconsistent reporting</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>No longer interested, but eligible</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>No show</td>
<td>n/a</td>
<td>8</td>
</tr>
<tr>
<td>Withdrew from study</td>
<td>n/a</td>
<td>0</td>
</tr>
<tr>
<td>Technical problems</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

*Note.* Tel = telephone; Gyne = gynecological exam; IUD = intrauterine device.

The thirty women (15 PVD and 15 controls) who completed the study were matched on parity (yes, no), hormonal contraceptive use (yes, no), and age (+/- 3 years). In order to be included in the PVD group, participants were required to meet criteria for a diagnosis of PVD during a standardized gynecological examination (see below), and to report pain symptoms for a minimum of six months, consistent with a more stringent definition of chronic pain. Participants in the control group were included if they reported pain-free intercourse and have an average pain rating of less than three on a Likert scale
during the cotton-swab-test portion of the standardized gynecological examination (see below). Exclusion criteria for both groups were: (1) current pregnancy; (2) diagnosis or history of hypertension, circulatory disorders, or other cardiac problems; (3) current use of any centrally acting medications (e.g., anti-depressants); (4) other chronic pain conditions; (5) major medical and/or psychiatric illness; (6) active vaginal infections; (7) concurrent gynecological problems; (8) surgical treatment involving the urogenital region; (9) less than a high school education; (10) left handedness; and (11) not meeting fMRI safety criteria (e.g., surgeries, piercings/tattoos, or implants that may interfere with the safety protocol in the fMRI facility; see Appendix D). Women were not tested at a particular point in their menstrual cycle due to scheduling limitations at the imaging center; however, the start date of their last period was recorded and analyses revealed no group differences in the phases at which they were tested, $t(28) = -2.92, ns (p = .77)$. A review study indicated that, although a number of studies report that pain responses vary across the menstrual cycle, an equal number of studies suggest that this is not the case (Sherman & LeResche, 2006).

4.2. Gynecological Examination

As mentioned above, women who were deemed eligible following the telephone screening were scheduled for an appointment in the Department of Obstetrics & Gynecology at Kingston General Hospital. Participants were provided a letter of information (Appendix F), a consent form (Appendix G), and a brief medical and pain history questionnaire (Appendix H). The consent form referred to the medical directive allowing trained graduate students, under Dr. Pukall’s supervision, to perform vulvar sensory testing. A copy of the directive was provided for participants upon request (Appendix I). Once consent was obtained, participants underwent a brief gynecological examination (5-10 minutes) conducted by the study gynecologist, Dr. Susan Chamberlain. The purpose of this examination was to confirm participant eligibility for the PVD or healthy control group. The examination involved a standardized protocol including a visual and manual examination of the external and internal reproductive
organs (Appendix J). As well, it consisted of a cotton-swab palpation of five areas of the vulvar vestibule (1, 4-5, 6, 7-8, and 11 o’clock), midline areas (between the urethra and the vaginal opening, the vaginal opening, the posterior fourchette, and the perineum), and the labia majora and minora (Appendix K). The cotton-swab test of the vulvar vestibule is the standard gynecological method for diagnosing PVD (Friedrich, 1987). The current study included cotton-swab palpations of the entire vulvar region in order to differentiate between women with PVD and those with generalized vulvodynia (GVD), a pain condition affecting a more widespread region of the external genitals. Prior to commencing the gynecological examination, participants were informed of their ability to control the pace of the examination and to terminate the examination at any point without question. A graduate student was present throughout the gynecological examination in order to record participant’s pain intensity ratings in response to the palpations. Participants were trained on a pain intensity rating scale prior to commencing the gynecological exam. The verbal ratings given by the participant were recorded as whole numbers on the numerical rating scale (0 = no pain, 1-3 = mild pain, 4-6 = moderate pain, 7-9 = severe pain, 10 = worst pain imaginable). This same pain intensity rating scale was used during sensory and fMRI testing; the participant was re-trained on the ratings prior to each new section of the study (see below).

4.3. Interview & Questionnaires

The structured interview (30 minutes) included questions pertaining to sociodemographic information, medical history, sexual and relationship functioning, and pain during intercourse and other activities (Appendix L). After the interview, participants remained in the SHRL testing room to complete the following questionnaires on a secure online computer program (Checkbox Survey, Prezza Technologies Inc., MA, USA; 30 minutes). Although the option to complete the measures on a hard copy was given to all women, all participants chose to complete the measures online.

(1) The Pain Catastrophizing Scale (PCS; Sullivan et al., 1995) is a 13-item measure consisting of descriptions of various thoughts and feelings people might experience related to pain. The respondent
indicates on a Likert-type scale of 0 (not at all) to 4 (all the time) how often they experience that particular thought or feeling when they are in pain. Scores range from 0 to 52, with higher scores indicating higher levels of catastrophizing. The PCS manual indicates that, although the scores on the PCS are normally distributed, a score of 30 can be thought of as a cut-off for clinically relevant catastrophizing. This scale has shown to be reliable and valid (Osman, Barrios, Kopper, Hauptmann, Jones, & O’Neill, 1997). This scale was administered to all women in relation to their most distressing non-vulvar pain, and again to women with PVD in relation to their vulvar pain. For this sample, high reliability was achieved for the control group, Cronbach’s $\alpha = .93$, and for PVD groups on vulvar and non-vulvar pain, Cronbach’s alphas were .92 and .96, respectively.

(2) The State-Trait Anxiety Scale (STAI-S & STAI-T; Spielberger, Gorusch, & Lushene, 1970) is a 40-item self-report measure that is divided into two sections, with 20 items measuring the transient condition of state anxiety and 20 items devoted to the long standing condition of trait anxiety. Responses are rated on a 4-point Likert scale, ranging from 1 (not at all) to 4 (very much so). Possible scores range from 20–80, with higher scores indicating greater anxiety (Low anxiety = 20–39, moderate anxiety = 40–59, high anxiety = 60–80). The STAI has been shown to be both reliable and valid (Spielberger, 1985). The state anxiety version was administered once during the interview and again prior to entering the fMRI machine. For this sample, high reliability was achieved for the control and PVD groups for trait anxiety, Cronbach’s alphas were .84 and .94, respectively. For state anxiety at the time of the interview, Cronbach’s alphas were .94 and .95, for control and PVD groups respectively. For state anxiety at the time of the fMRI session, Cronbach’s alphas were .88 and .91, respectively for the control and PVD groups.

(3) The Anxiety Sensitivity Index-3 (AS1-3; Taylor et al., 2007) is based upon the original anxiety sensitivity index (Reiss, Peterson, Gursky, & McNally, 1986), but with improved psychometric properties. The AS1-3 is a reliable and valid (Taylor et al., 2007) 18-item measure of fear of anxiety symptoms broken down into three factors: physical, cognitive, and social concerns. Items are rated on a 5
point scale ranging from (0) very little to (4) very much. Scores range from 0-64, with higher scores reflecting higher levels of anxiety sensitivity. For the current sample, high reliability was achieved for the control and PVD groups, Cronbach’s alphas were .92 and .94, respectively.

(4) The Pain Anxiety Symptoms Scale - 20 (PASS-20; McCracken & Dhingra, 2002) is a 20-item measure assessing anxiety and fear of pain, which was developed from the original 40-item measure (McCracken, Zayfert, & Gross, 1992). The PASS consists of four subscales measuring somatic/physiological anxiety, cognitive anxiety, fear, and escape/avoidance. Each item is answered on a 7 point Likert scale with 0 representing “never” and 6 representing “always”. Scores on the PASS range from 0 to 120, with higher scores representing greater anxiety. Psychometric properties of the original PASS were maintained (McCracken & Dhingra, 2002). For example, the PASS-20 shows good reliability on the total score ($\alpha = .83$) and subscales (Coons, Hadjistavropoulous, & Asmundson, 2004). The PASS-20 has a high Pearson correlation coefficient ($r = .98$) with the original PASS (Roelofs, McCracken, Peters, Crombez, Van Breukelen, & Vlaeyen, 2004). The PASS-20 also demonstrated validity through high correlations with other fear and anxiety measures such as the ASI and the MPI. The PASS-20 was used in the current study to assess fear of pain. For the current sample, high reliability was achieved for the control group ($\alpha = .97$). High reliability was also achieved for non-vulvar PASS ($\alpha = .93$) and the vulvar PASS, ($\alpha = .90$) in the PVD group.

(5) The Pain Vigilance and Awareness Questionnaire (PVAQ; McCracken, 1997) is a 16-item measure of awareness, vigilance, preoccupation, and observation of pain. Participants respond on a 6 point scale (0 = never; 5 = always) based on their frequency of behaviours over the last 2 weeks. Scores range from 0 to 80, with higher scores representing higher levels of pain vigilance. This measure has good internal consistency ($\alpha = .86$) and has been validated for use with chronic pain and healthy samples (McWilliams & Asmundson, 2001). The PVAQ is correlated with the PCS and the PASS (Roelofs, Peters, McCracken, Vlaeyen, 2003). For the current sample, high reliability was achieved for the
control group, ($\alpha = .96$). High reliability was also achieved for non-vulvar PVAQ ($\alpha = .94$) and the vulvar PVAQ, ($\alpha = .93$) in the PVD group.

(6) **The Female Sexual Function Index** (FSFI; Rosen et al., 2000) is a 19-item measure assessing six domains of sexual functioning: desire, arousal, lubrication, orgasm, satisfaction, and pain. The FSFI has been validated on control women as well as women with sexual dysfunctions. It has proven to be a reliable measure, with both clinical and psychometric validity. Individual subscale scores can reach a maximum of 6 while total scores range up to 36, with higher scores indicating better sexual function. A total score under 26.55 suggests the presence of clinically significant sexual difficulties (Wiegel, Meston, & Rosen, 2005). For the current sample, high reliability was achieved for the control and PVD groups, Cronbach’s $\alpha = .95$ and .93, respectively.

(7) **The Sexual Self-Efficacy Scale for Female Function** (SSES-F; Creti et al., 1989) is a 37-item measure assessing a woman’s perceived competence in the behavioural, cognitive, and affective dimensions of female sexual response. For each item, respondents indicate whether they can do the activity, and if so, how confident they are that they can engage in the activity. Confidence rating scores range from 10 (quite uncertain) to 100 (quite certain), with higher scores indicating higher sexual self-efficacy. Activities that the respondent does not check as being able to do are rated as zero. The SSES-F shows good internal consistency ($\alpha = .93$) and has been validated against other measures of sexual functioning. For the current sample, high reliability was achieved for the control and PVD groups, Cronbach’s alphas were .97 and .94, respectively.

4.4. **Quantitative Sensory Testing**

Prior to starting the sensory testing session, participants were familiarized with the testing materials and explicitly debriefed as to the QST procedures. Participants were reminded that they would be in control of the session and that they were able to stop testing at anytime throughout the procedure. Pressure pain thresholds were measured at the six o’clock position of the vulvar vestibule. All of the QST
was performed by the author of the thesis, who holds a medical delegation to perform such testing at the vulvar vestibule (see Appendix I). In order to measure pressure pain thresholds, a set of 5 non-magnetic vulvalgesiometers (Appendix M), which exert pressures ranging from 3g to 950g, was used (Pukall, Young, Roberts, Sutton, & Smith, 2007). Each time pressure was applied, participants were asked to rate the intensity using the scale described above. Pressure was increased manually until the participants indicated that the sensation of touch turned to a painful sensation, indicating pain threshold. The pain intensity rating and amount of pressure applied was recorded. The pressure stimuli continued to be applied until the participant rating reached a moderate level (4/10). The pressure associated with this moderate pain threshold was recorded. This QST procedure was repeated prior to each of the three experimental sessions in the fMRI protocol in order to adapt for any changes in sensitivity experienced by the participant over time. The aim of the current study was to maintain a pain rating of 4/10 during the pain trials, rather than a constant force of applied pressure.

4.5. Psychosocial and Psychophysical Data Analysis

Analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 19. The significance level was set at $p < .05$ and data were expressed as mean +/- standard deviation. Between group differences were conducted using chi-squares, t-tests, and ANOVAs.

4.6. fMRI Testing Session

The current study examined changes in concentration of oxygen in the blood using BOLD contrast, which is an indirect measure of neuronal activity. The BOLD method identifies differences in the ratio of deoxyhemoglobin to oxyhemoglobin during a particular task as compared with a baseline. The hemodynamic response function (HRF) describes the temporal BOLD response to a specific stimulus (Heeger & Ress, 2002).
4.6.1. **Image Acquisition**

Images were acquired using a 3.0 Tesla Siemens Trio MRI scanner at the Queen’s Centre for Neuroscience Studies MRI Facility in Kingston, Ontario, Canada. Anatomical scans were recorded using a high resolution T1-weighted anatomical protocol with a resolution of 1 x 1 x 1 mm. Functional scans were collected using a T2*-weighted gradient echo-planar imaging sequence (TR = 2000 ms; TE = 30 ms; flip angle 78 deg) with interleaved slice acquisition. The voxel volume used was 3 x 3 x 3 mm. A total of 837 scans were collected from participants over three scanning runs (279 scans per run). Each run consisted of six experimental conditions, presented six times each, resulting in a total of 18 images per condition over the course of the whole experiment. Conditions were pseudo-randomized within each run. The pseudo randomization ensured an equal number of conditions per run, as well as controlling for sensitization and habituation by ensuring that a pain pressure condition was never administered subsequent to another pain pressure condition. The three runs were presented in random order between participants.

4.6.2. **Preprocessing**

fMRI data were processed and analyzed using Statistical Parametric Mapping version 8 (SPM8; Wellcome Department of Cognitive Neuroscience, London, UK). The first volume of each run was discarded. Data preprocessing steps for each subject included: (1) rigid realignment of each echo planar image (EPI) volume to the first of each session; (2) trimming with origin set at the anterior commissure; (3) coregistration of the structural image to the mean EPI; (4) normalization of the structural image to MNI space using SPM8; (5) warping of all EPI volumes, including re-sampling to a voxel size of 3.0 mm³; and (6) spatial smoothing using a Gaussian kernel with a full-width at half maximum (FWHM) of 6 mm. A 128 second high-pass filter was applied. Quality assurance checks for data artifacts were conducted using the tsdiffana and ART toolboxes. Subjects were checked for movement of greater than 2 voxels. To account for effects of movement, the estimated movement parameters were included in the
statistical analysis. Outliers were excluded in the statistical analysis; regressors for the outliers were generated by the ART toolbox. The contrast comparing painful stimuli to no stimuli was examined for each subject as a quality control check to ensure valid models and data. All participants displayed activation throughout the pain matrix, and thus were included in further analyses.

4.6.3. Neuroimaging Data Analysis

4.6.3.1. First Level Analysis

Analysis at the first level (single subject fixed-effects) was conducted using the General Linear Model (GLM). Each scan was coded as belonging to one of six experimental conditions or to a seventh condition encompassing all of the scans associated with the rating scale, which subjects viewed after each condition. Contrast images were generated for each of the six conditions. In addition, contrasts for the simple effects of pressure were conducted at the individual subject level, resulting in three contrasts of activation for each subject: (1) pain-baseline; (2) touch-baseline; and (3) pain-touch. There were also three contrasts for areas of deactivation for each subject: (1) baseline-pain; (2) baseline-touch; and (3) touch-pain. The three runs were modeled as one session within the design matrix, and three regressors were used to code for each of the runs. As noted in the pre-processing section, six realignment parameters were included for movement-related effects (x, y, z, pitch, yaw, and roll), along with additional regressors from the ART toolbox pre-processing to account for outliers based on a cut off of greater than 2 voxels of movement. Serial correlations were corrected using an autoregressive model. Peak points of activation were labeled using Anatomy Toolbox. In cases where there was no label available, this was indicated and the LONI probabilistic brain atlas (LPBA40; Shattuck et al., 2008) was used. The results of the fMRI analyses are shown on the averaged, normalized T-1 weighted structural image of the participants in the current study.
4.6.3.2. Study One Second-Level Analysis

The contrast images from each subject, one for each of the six experimental conditions, were entered into a second-level random-effects analysis. A 2x2x3 mixed-model ANOVA (group x word x pressure) was performed using the full-factorial second-level batch script in SPM8. *F*-contrasts were used to assess the overall main effects of group, word, pressure, and their interactions (see Appendix A). Peaks with more than one voxel that were statistically significant at the whole-brain level using family-wise error correction for Type 1 error (FWE, *p* < .05) were reported. Simple main effects were conducted using second level two-sample *t*-tests at *p* < .05, FWE. Peaks were localized and labeled using the probabilistic anatomical map available in the SPM Anatomy Toolbox (Eickhoff et al., 2005). For significant peak points corresponding to the *a priori* determined areas of interests (e.g., those identified as being a part of the pain matrix), the simple effects and interactions were plotted. To maximize power for interaction effects, functionally determined small volume corrections (SVC) within the pain-matrix were conducted at a FWE corrected threshold of *p*<.05. SVCs were created using a combination of 180 other studies examining pain, obtained from Neurosynth.org, a website that has conducted large-scale synthesis of fMRI data extracted from published articles. The pain matrix SVC was created from an image generated by Topic 64 on the neurosynth.org website. The SVC image contained areas associated with both activations and deactivations.

*Simple Effects of Pressure.* Contrast images were generated at the single-subject level by comparing the condition parameter estimates (i.e., betas) to examine areas of activation and deactivation during pain and touch stimuli. The (pain-touch), (pain-none), (touch-none), (none-pain), (none-touch), and (touch-pain) contrast images from each subject were entered into second level random effects analysis to examine whether there were group differences in these *a priori* determined simple effects.

*Simple Effects of Word.* As per *a priori* hypotheses, second level *t*-tests were conducted for the first level contrast comparing painful and neutral words during the no pressure condition.
Explorations of Group x Pressure Interaction. Based on the hypothesis that pain and touch would look more similar for women with PVD than for control women, parameter estimates of peak points within the pain matrix were extracted and groups were compared on the difference scores between the parameter estimates associated with pain minus those associated with touch.

4.6.3.3. Study Two

The subject-level contrast images comparing pain to no pressure were entered into a second level random effects analysis. Group mean-centered covariates of interest were included in second-level between group t-tests. Correlations were conducted between brain activity during painful stimulation and the following psychosocial variables: (1) anxiety, as measured by the STAI-T; (2) attention and hypervigilance, as measured by the PVAQ; (2) catastrophizing, as measured by the PCS. For the first set of analyses, the groups used in the comparison were women with PVD and control women. The second set of analyses examined differences between high and low scorers on the psychosocial measures, regardless of whether they were classified in the PVD or control group. Lastly, the PCS and PVAQ were entered simultaneously as group mean-centered covariates in SPM8, and each variable was examined for correlations with neural activation, while controlling for the other variable to determine whether there were unique effects of anxiety or catastrophizing. Whole brain correlation analyses were conducted at a threshold of $p < .001$, uncorrected for clusters of more than one voxel.

4.6.3.4. Study Three

The subject-level contrast images comparing pain to no pressure were entered into a second level random effects analysis, and second-level $t$-tests were conducted to examine differences between the primary and secondary PVD groups for neural activations and deactivations associated with painful stimuli. A covariate of pain duration was included in the analyses, as pain duration has been reported to be a confounding variable when comparing these two subgroups. As this was an exploratory analysis with
few participants in each group, whole brain analyses were conducted at a threshold of \( p < .001 \), uncorrected.

4.6.4. fMRI Experimental Procedures

The experimental procedures were identical for all three studies. Once in the scanning room, women were asked to undress from the waist down. They were given earplugs to wear and their heads were immobilized by foam pads attached to the head coil. In order to conduct the sensory testing, participants bent their knees and rested them against the outside curve of the tunnel, exposing the posterior portion of the vulvar vestibule for pressure applications. At this point, sensory testing was conducted with vulvalgesiometers at the vulvar vestibule to assess pressure pain and moderate pain thresholds. In addition, a minimum of six practice trials were conducted to ensure that the participant understood the task, and that they were able to provide verbal pain ratings with minimal movement of the head. Participants were then covered with a blanket for the anatomical scan. During this time they were instructed not to move. They were assured that there would be no stimuli applied for this first scan. This scan was followed by three sessions of testing during functional scanning. Each session was preceded by QST for pain threshold and moderate pain threshold (described above), and followed by a 5 minute rest period during which there was no scanning or testing. Each session consisted of continuous scanning of 36 trials, in which one of six conditions was administered. In order to apply pressure to the vulvar vestibule, the labia must be held open. During the trials in which no pressure was applied the experimenter was still holding the edges of the labia; however, no pressure was applied to the vulvar vestibule. The consistent pressure to the labia throughout the experiment ensured that the applied pressure to the vulvar vestibule was not confounded by additional pressure applied to the labia each time a pressure stimulus was to be applied. As BOLD is impacted by the introduction or removal of a stimulus, the constant application of pressure was not anticipated to result in trial-specific changes to neuronal activity.
The experimental paradigm was designed for study 1; studies 2 and 3 used the specific scans from the experimental paradigm associated with the trials in which the participant experienced painful stimuli (pain trials with both types of word were used). The first experiment was a mixed model 2x2x3 factorial design, which compared two groups (PVD and control participants) and paired two types of word primes (pain and neutral adjectives; Appendix N) with three types of pressure stimuli (pain, touch, none). Word primes were presented 1000ms prior to the pressure stimuli for a duration of 1000ms. The pressure stimuli were applied for a total of 2000ms. A rating scale appeared 4000ms following the onset of pressure stimuli and remained on the screen for 5000ms, during which time participants were instructed to verbally provide a pain intensity rating for the sensation that was just experienced. Each trial lasted a total of 10 seconds from presentation of the word stimulus to the end of the rating scale. Trials were followed by a variable inter-stimulus interval (ISI) of 3, 5, or 7 seconds (see Appendix O). The use of a variable ISI to stagger stimulus presentation helped to control for anticipation of stimuli, and helped to de-couple the experimental BOLD activation from low-frequency noise. The total time for each session was 9 minutes. The total time for the entire experiment, beginning from the structural scan and including rest between sessions was 38 minutes. The approximate total time in the scanner room, including QST and practice trials was one hour. See Appendix P for the design matrix and Appendix Q for the stimulus programming file.

The experimental stimuli consisted of the presentation of six pain words, which were adjectives chosen based on the most common descriptors used to describe vulvar pain by women with PVD on the McGill Pain Questionnaire (MPQ; Melzack, 1975), as determined during the author’s MA thesis study (Sutton, 2007). Six neutral adjectives were presented and matched to the six pain words in length. Each adjective was presented three times per session, with two adjectives assigned to each of the six conditions. Each word presentation was paired with a pressure stimulation (applied one second later). All pressure stimulations were followed by a pain intensity rating scale. For conditions in which no pain was experienced, participants were asked to report a rating of zero. Painful pressures were administered to
evoke a painful sensation with an intensity rating of 4 out of 10. Touch pressures were administered using 3g of pressure for all participants, which is the minimum amount of pressure evoked by the vulvalgesiometer. All participants reported experiencing touch sensation at this pressure level during the QST.
Chapter 5. Results

5.1. Participant Characteristics

Thirty women (15 PVD and 15 controls) took part in the study. There were no significant differences on any of the demographic variables (see Table 2).

Table 2

Means (M), Standard Deviations (SD), and Percentages on Demographic Variables

<table>
<thead>
<tr>
<th></th>
<th>PVD</th>
<th>Control</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 15)</td>
<td>(N = 15)</td>
<td></td>
</tr>
<tr>
<td><strong>M (SD) / N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>22.13 (4.47)</td>
<td>22.33 (4.62)</td>
<td>( t(28) = .12, \text{ ns} )</td>
</tr>
<tr>
<td>OC use (% yes)</td>
<td>11 (73%)</td>
<td>12 (80%)</td>
<td>( \chi^2(1, N=30) = .19, \text{ ns} )</td>
</tr>
<tr>
<td>OC duration (months)</td>
<td>29.40 (43.50)</td>
<td>22.83 (39.54)</td>
<td>( t(28) = -.43, \text{ ns} )</td>
</tr>
<tr>
<td>Parity (yes)</td>
<td>1 (7%)</td>
<td>1 (7%)</td>
<td>-</td>
</tr>
<tr>
<td>Relationship status (% in a relationship)</td>
<td>11 (73%)</td>
<td>12 (80%)</td>
<td>( \chi^2(1, N=30) = .19, \text{ ns} )</td>
</tr>
<tr>
<td>Relationship duration (months)</td>
<td>46.53 (51.66)</td>
<td>36.53 (35.88)</td>
<td>( t(28) = -.62, \text{ ns} )</td>
</tr>
<tr>
<td>Sexual orientation (heterosexual)</td>
<td>13 (87%)</td>
<td>15 (100%)</td>
<td>( \chi^2(2, N=30) = 2.14, \text{ ns} )</td>
</tr>
<tr>
<td>Education (years of postsecondary)</td>
<td>3.40 (1.24)</td>
<td>4.03 (1.28)</td>
<td>( t(28) = 1.37, \text{ ns} )</td>
</tr>
<tr>
<td>Religious (yes)</td>
<td>10 (67%)</td>
<td>11 (73%)</td>
<td>( \chi^2(1, N=30) = .16, \text{ ns} )</td>
</tr>
</tbody>
</table>

Note. * OC = Oral contraceptive.
In addition to the above information, women with PVD were asked to report on their vulvar pain (see Table 3).

Table 3

*Means (M), Standard Deviations (SD), Percentages, and Ranges of pain variables for women with PVD*

<table>
<thead>
<tr>
<th></th>
<th>M (SD) / N (%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first pain</td>
<td>18.10 (1.68)</td>
<td>15-20</td>
</tr>
<tr>
<td>Pain duration (years)</td>
<td>4.00 (4.33)</td>
<td>0.67-17</td>
</tr>
<tr>
<td>% women with primary PVD</td>
<td>6 (43%)</td>
<td>-</td>
</tr>
<tr>
<td>% women who consulted a health professional</td>
<td>7 (47%)</td>
<td>-</td>
</tr>
<tr>
<td>Number of health professionals</td>
<td>2.71 (2.36)</td>
<td>1-8</td>
</tr>
<tr>
<td>% of time intercourse is painful</td>
<td>83 (18.4)</td>
<td>50-100</td>
</tr>
<tr>
<td>How long pain lasts after intercourse (hours)</td>
<td>2.23 (6.31)</td>
<td>0-24</td>
</tr>
<tr>
<td>Average pain intensity (intercourse 0-10)</td>
<td>5.93 (1.91)</td>
<td>3-10</td>
</tr>
<tr>
<td>Average pain unpleasantness (intercourse 0-10)</td>
<td>6.20 (2.14)</td>
<td>3-10</td>
</tr>
</tbody>
</table>

During the interview, women with PVD and control women were asked a series of questions about their health and physical functioning (see Table 4).
### Table 4

*Means (M), Standard Deviations (SD), and Percentages of Health and Physical Functioning Variables*

<table>
<thead>
<tr>
<th></th>
<th>PVD M (SD)/ N (%)</th>
<th>Control M (SD)/ N (%)</th>
<th>t</th>
<th>p</th>
<th>Effect size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean pain intensity during menstruation (0-10)</td>
<td>2.33 (1.84)</td>
<td>1.53 (1.41)</td>
<td>-2.94</td>
<td>.007</td>
<td>.49*</td>
</tr>
<tr>
<td>Mean unpleasantness during menstruation (0-10)</td>
<td>1.73 (1.62)</td>
<td>2.47 (1.64)</td>
<td>-3.07</td>
<td>.005</td>
<td>.45*</td>
</tr>
<tr>
<td>Number of yeast infections</td>
<td>2.40 (2.87)</td>
<td>2.2 (3.59)</td>
<td>-0.17</td>
<td>Ns</td>
<td>.07</td>
</tr>
<tr>
<td>Number of UTIs</td>
<td>2.07 (5.13)</td>
<td>2.00 (3.02)</td>
<td>-0.04</td>
<td>Ns</td>
<td>.02</td>
</tr>
<tr>
<td>Chronic pain diagnosis (yes)</td>
<td>1 (7%)</td>
<td>1 (7%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Number of self-reported ailments</td>
<td>4.60 (2.55)</td>
<td>4.07 (3.00)</td>
<td>-0.53</td>
<td>Ns</td>
<td>.21*</td>
</tr>
<tr>
<td>Intensity rating of worse ailment (0-10)</td>
<td>6.13 (2.41)</td>
<td>5.21 (2.72)</td>
<td>-0.96</td>
<td>Ns</td>
<td>.38*</td>
</tr>
<tr>
<td>Intensity of body pain in last month (0-6)</td>
<td>2.87 (1.06)</td>
<td>2.53 (1.06)</td>
<td>-0.86</td>
<td>Ns</td>
<td>.34*</td>
</tr>
<tr>
<td>Interference of body pain with ADLs in last month (0-6)</td>
<td>2.00 (1.46)</td>
<td>1.53 (0.99)</td>
<td>-1.02</td>
<td>Ns</td>
<td>.40*</td>
</tr>
</tbody>
</table>

*Note.* UTI = urinary tract infection; ADL = activities of daily living; * = small effect (0.2); ** = medium effect (0.5); *** = large effect (0.8; Cohen, 1988).

### 5.2. Sexuality Variables

The participants were also asked about their sexual and relationship history (see Table 5).
Table 5

*Means (M), Standard Deviations (SD), Percentages of Sexual and Relationship History Variables*

<table>
<thead>
<tr>
<th></th>
<th>PVD</th>
<th>Control</th>
<th>t</th>
<th>p</th>
<th>Effect size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)/N (%)</td>
<td>M (SD)/N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain at first intercourse (0-10)</td>
<td>5.40 (3.62)/2.07 (2.49)</td>
<td>-2.94/.007</td>
<td></td>
<td>1.07***</td>
<td></td>
</tr>
<tr>
<td>Unpleasantness of first</td>
<td>4.93 (3.43)/1.67 (2.29)</td>
<td>-3.07/.005</td>
<td></td>
<td>1.12***</td>
<td></td>
</tr>
<tr>
<td>intercourse (0-10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of sexual partners</td>
<td>5.60 (4.47)/4.87 (4.09)</td>
<td>-0.47/ ns</td>
<td></td>
<td>.17</td>
<td></td>
</tr>
<tr>
<td>Average number of intercourse</td>
<td>12.3 (7.63)/15.0 (9.32)</td>
<td>0.87/ ns</td>
<td></td>
<td>.34*</td>
<td></td>
</tr>
<tr>
<td>attempts per month (in last 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent of time foreplay leads</td>
<td>83.21 (15.01)/80.33 (17.57)</td>
<td>-0.66/ ns</td>
<td></td>
<td>.26*</td>
<td></td>
</tr>
<tr>
<td>to intercourse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent of the time participant</td>
<td>40.80 (26.76)/44.67 (18.66)</td>
<td>0.46/ ns</td>
<td></td>
<td>.18</td>
<td></td>
</tr>
<tr>
<td>initiates sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confidence initiating sex (0-10)</td>
<td>7.86 (3.03)/8.89 (1.08)</td>
<td>1.20/ ns</td>
<td></td>
<td>.47*</td>
<td></td>
</tr>
<tr>
<td>Confidence when partner</td>
<td>7.47 (2.56)/9.23 (1.08)</td>
<td>2.46/.024</td>
<td></td>
<td>.90***</td>
<td></td>
</tr>
<tr>
<td>initiates sex (0-10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Happy with percent of time</td>
<td>13 (93%)/13 (93%)</td>
<td>-/-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>foreplay leads to intercourse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Happy with intercourse frequency (yes)</td>
<td>11 (79%)/13 (93%)</td>
<td>1.17/ ns</td>
<td></td>
<td>.42*</td>
<td></td>
</tr>
</tbody>
</table>

*Note. * = small effect (0.2); ** = medium effect (0.5); *** = large effect (0.8; Cohen, 1988).*
Women were also asked what types of sexual activities they engaged in and whether or not this activity regularly resulted in pain. None of the activities regularly resulted in pain for the control women, thus just the data from the PVD group is reported in Table 6. There were no significant group differences in the number of women who engaged in each activity; the only exception was that of anal play/sex with the participant as the receiver. Four of 15 control women reported this activity, as compared to 0/15 women with PVD, $X^2(1, N=29) = 4.33, p = .037$.

Table 6

*Percentages of Women with PVD Engaging in and Experiencing Pain During Sexual Activities*

<table>
<thead>
<tr>
<th>N (%) of women who engage in activity</th>
<th>N (%) of women who experience pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kissing</td>
<td>15 (100)</td>
</tr>
<tr>
<td>Non-genital touching</td>
<td>15 (100)</td>
</tr>
<tr>
<td>Touching partner’s genitals</td>
<td>15 (100)</td>
</tr>
<tr>
<td>Partner touching your genitals</td>
<td>15 (100)</td>
</tr>
<tr>
<td>Giving oral sex</td>
<td>15 (100)</td>
</tr>
<tr>
<td>Receiving oral sex</td>
<td>14 (93)</td>
</tr>
<tr>
<td>Anal play/sex on partner</td>
<td>0</td>
</tr>
<tr>
<td>Anal play/sex on you</td>
<td>0</td>
</tr>
</tbody>
</table>

Women were also asked to report on their sexual functioning. Women with PVD have consistently demonstrated lower sexual functioning than control women. The following study examined sexual functioning using the FSFI. Although this variable will not be examined in the context of the neuroimaging section of the study, it was included as a check to ensure that the PVD group was similar to those groups studied generally in the literature. Women with PVD reported greater levels of sexual
dysfunction as compared with control women ($p < .001$). On the subscales, they reported lower levels of arousal ($p < .01$), lubrication ($p < .05$), and satisfaction ($p < .05$), as well as higher levels of pain ($p < .001$) as compared with control participants. On the SSES, a measure examining sexual self-efficacy, the total score was not significantly different between groups. When examining subscales, women with PVD had significantly lower self-efficacy in the area of sexual desire ($p < .05$) and a trend toward lower self-efficacy in orgasm ($p = .07$). As indicated in Table 7, there were no significant group differences on the other subscales.

Examination of group differences in psychosocial and psychophysical variables was conducted using $t$-tests, chi-square, and MANOVAs. Within-groups analyses for the psychosocial variables were conducted using multiple regression techniques. For the analysis concerning BOLD activation and the fMRI portion of the thesis, please refer to the detailed outline below.
Table 7

*Means (M) and Standard Deviations (SD) of Sexuality Measures*

<table>
<thead>
<tr>
<th>Measure</th>
<th>PVD M (SD)</th>
<th>Control M (SD)</th>
<th>F</th>
<th>p</th>
<th>Effect size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSFI desire</td>
<td>3.64 (1.10)</td>
<td>4.08 (.79)</td>
<td>0.45</td>
<td>.51</td>
<td>.46*</td>
</tr>
<tr>
<td>FSFI arousal</td>
<td>3.92 (1.13)</td>
<td>5.31/.68</td>
<td>17.29</td>
<td>.001</td>
<td>1.49***</td>
</tr>
<tr>
<td>FSFI lubrication</td>
<td>3.84 (.83)</td>
<td>4.50 (.59)</td>
<td>4.71</td>
<td>.04</td>
<td>.92***</td>
</tr>
<tr>
<td>FSFI orgasm</td>
<td>3.80 (1.93)</td>
<td>4.80 (1.50)</td>
<td>2.68</td>
<td>.12</td>
<td>.58**</td>
</tr>
<tr>
<td>FSFI satisfaction</td>
<td>3.86 (1.42)</td>
<td>4.97 (1.38)</td>
<td>5.23</td>
<td>.03</td>
<td>.79**</td>
</tr>
<tr>
<td>FSFI pain</td>
<td>2.37 (1.24)</td>
<td>5.69 (.48)</td>
<td>74.85</td>
<td>.001</td>
<td>3.53***</td>
</tr>
<tr>
<td>FSFI total</td>
<td>21.82 (4.58)</td>
<td>29.54 (2.58)</td>
<td>26.20</td>
<td>.001</td>
<td>2.08***</td>
</tr>
<tr>
<td>SSES orgasm</td>
<td>6.11 (2.21)</td>
<td>7.64 (2.23)</td>
<td>3.54</td>
<td>.07</td>
<td>.69**</td>
</tr>
<tr>
<td>SSES desire</td>
<td>6.68 (2.52)</td>
<td>8.53 (1.53)</td>
<td>5.96</td>
<td>.02</td>
<td>.89***</td>
</tr>
<tr>
<td>SSES sensuality</td>
<td>8.24 (2.16)</td>
<td>8.40 (2.50)</td>
<td>0.03</td>
<td>.86</td>
<td>.07</td>
</tr>
<tr>
<td>SSES arousal</td>
<td>6.30 (2.70)</td>
<td>7.61 (2.20)</td>
<td>2.14</td>
<td>.15</td>
<td>.53**</td>
</tr>
<tr>
<td>SSES affection</td>
<td>8.38 (1.92)</td>
<td>8.38 (1.86)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SSES communication</td>
<td>7.15 (2.56)</td>
<td>7.89 (2.30)</td>
<td>0.71</td>
<td>.41</td>
<td>.30*</td>
</tr>
<tr>
<td>SSES body accept</td>
<td>6.73 (3.26)</td>
<td>8.00 (2.46)</td>
<td>1.45</td>
<td>.24</td>
<td>.52**</td>
</tr>
<tr>
<td>SSES refusal</td>
<td>6.10 (3.04)</td>
<td>7.03 (2.92)</td>
<td>0.74</td>
<td>.40</td>
<td>.32*</td>
</tr>
<tr>
<td>SSES total</td>
<td>6.93 (1.82)</td>
<td>7.99 (1.90)</td>
<td>2.05</td>
<td>.16</td>
<td>.57**</td>
</tr>
</tbody>
</table>

*Note.* * = small effect (0.2); ** = medium effect (0.5); *** = large effect (0.8; Cohen, 1988).
5.3. Gynecological Examination

Consistent with previous findings (e.g., Pukall et al., 2002; Sutton, 2007), women in the PVD group reported significantly higher pain intensity ratings ($M = 4.69, SD = 1.63$) during the cotton-swab test of the vulvar vestibule than control women ($M = .86, SD = .91$), $t(28) = -7.94, p < .001, d = 2.90$.

5.4. Quantitative Sensory Testing

Figure 3 shows the results for the group pressure pain thresholds. Consistent with previous findings (Pukall et al., 2002; Sutton, 2007), women with PVD exhibited a significantly lower pressure pain threshold than control women ($M = 24.86, SD = 17.17$, range = 3-50; $M = 77.14, SD = 64.08$, range = 15-200, respectively), $t(14.9) = 2.95, p = .01$. Figure 3 also shows the group pressures associated with an intensity rating of 4/10. This measure was taken on 4 occasions during the experiment, and the figure is the data of the average pressure of the four measurement points. For women with PVD, pain ratings of a 4/10 were associated with lower pressures ($M = 136.70, SD = 73.50$, range = 17.5 – 252.5) than for control women ($M = 279.82, SD = 172.93$, range = 31.25-650.00), $t(17.5) = 2.85, p = .01$. For each participant, a difference score was calculated to examine the amount number of grams between a rating of 1/10 and a rating of 4/10. There was a trend suggesting that control women tolerated higher increases from pressure pain threshold to moderate pain ($M = 202.68; SD = 150.53$) than did women with PVD ($M = 111.84; SD = 71.67$), $t(26) = 2.04, p = .052$. 

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Figure 3. Pressure pain thresholds (PPT) and moderate pressure pain thresholds (MPT) for women with PVD and control women, demonstrating lower PPTs and lower MPT for women with PVD as compared with control women. PPT is the point at which pain is first experienced and MPT is the point at which a 4/10 rating is provided by the participant.

5.5. Study #1

An examination of the contrast comparing pain to no pressure was examined in each participant, and served as a validation check that the experiment was modeled correctly. Each participant had widespread activation in the brain with significant activations in all of the areas of the pain matrix. There were significant main effects for group and pressure, but not for word type (Table 8).
Table 8

Main Effects of the Group-Level Mixed-Model ANOVA at the Whole-Brain Level, $p<.05$, FWE.

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Note. Peaks are significant at p < .05 FWE. ME = Main Effect, L = left, R = right, IPC = Inferior Parietal Cortex, ACC = Anterior Cingulate Cortex.

5.5.1. **Main Effect of Group**

The contrast assessing main effect of group at the whole brain revealed significant activations in the right temporal pole and right precentral gyrus (p < .05, FWE; see Table 9), with greater activation of these areas in the control group, as compared with the PVD group (see Figure 4).
5.5.2. Main Effect of Pressure

There was a statistically significant main effect of pressure across areas of the pain matrix when collapsed across word type and group (see Table 8 & Figure 5). In order to examine parameter estimates of pain, touch, and no pressure, graphs were created for peak points within the pain matrix, including the somatosensory regions (S1 & S2), the ACC, and areas of the PFC (see Figure 5). In many areas, pain and touch were associated with greater activation than no pressure. In the right postcentral gyrus, a cytoarchitectic region associated with S1, pain and touch were not significantly different from one another, but both had greater activations than no pressure. In the left supramarginal gyrus (OP1), an area associated with S2, pain and touch were not significantly different from one another, but both had significantly greater activations than no pressure. In the left ACC, pain was associated with greater activation than touch, which was associated with greater activation than none. There was no significant

Figure 4. Mean contrast values of control women and women with PVD at the right precentral gyrus, demonstrating greater activation for control women compared to women with PVD.
main effect of pressure in the insula, amygdala, thalamus, cerebellum, or hippocampus. For areas of the PFC, some of the main effects were being driven by activations in which pain resulted in greater activation than touch, which resulted in greater activation than none (e.g., right middle frontal gyrus; Figure 5); however, other areas were being driven by deactivations in which pain demonstrated greater deactivation than touch and none, and touch demonstrated greater deactivation than none (e.g., left middle orbital gyrus).

An analysis of the activations and deactivations associated with pain and touch was conducted using group-level t-tests (Table 9). Contrasts were examined across and between groups at the whole brain level, $p < .05$, FWE. There were no significant group differences in any of the contrasts. Figure 6 displays areas of activation associated with painful, touch, and no pressure conditions. Figure 7 displays areas of deactivation associated with painful and touch stimuli.
Figure 5. Main Effect of Pressure in a whole-brain analysis ($p < .05$, FWE). The colour scale represents F-values, which range from the critical F-value associated with a ($p < .05$, FWE) cut-off ($F = 14.35$) to the highest F-value obtained in this contrast ($F = 128.32$). On the depiction of the brain, the colours toward the red end of the spectrum indicate higher F scores (e.g., higher magnitudes of activation). Graphs (from upper right clockwise) depict activations for painful stimuli, touch stimuli, and no pressure in the right postcentral gyrus, the left supramarginal gyrus (OP1), the left ACC, the right middle orbital gyrus, and the right middle frontal gyrus. The latter three graphs depict areas where pain > touch > no pressure, while the first two graphs depict areas where pain = touch > no pressure.
Table 9

Peak Activation and Deactivation Results of Pressure Stimuli Using Whole-Brain Data, p<.05, FWE.

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<td>6  -81 12</td>
<td>4.94</td>
<td></td>
<td>R Calcarine Fissure - Area 18</td>
</tr>
<tr>
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<td>15   -72 12</td>
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</tr>
<tr>
<td></td>
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<td>5.12</td>
<td>3</td>
<td>L Precentral Gyrus - Area 6</td>
</tr>
<tr>
<td></td>
<td>54  -60 0</td>
<td>5.00</td>
<td>3</td>
<td>R Middle Temporal Gyrus</td>
</tr>
<tr>
<td></td>
<td>-15  -69 9</td>
<td>4.86</td>
<td>2</td>
<td>R Calcarine Fissure - Area 17</td>
</tr>
<tr>
<td>Touch-Pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>None-Pain</td>
<td>54   -54 24</td>
<td>7.50</td>
<td>116</td>
<td>R Angular Gyrus IPC (PGa)</td>
</tr>
<tr>
<td></td>
<td>60   -3  -18</td>
<td>7.27</td>
<td>51</td>
<td>R Middle Temporal Gyrus</td>
</tr>
<tr>
<td></td>
<td>-45  -57 24</td>
<td>6.60</td>
<td>53</td>
<td>L Angular Gyrus</td>
</tr>
<tr>
<td></td>
<td>3    45  -15</td>
<td>6.34</td>
<td>102</td>
<td>R Rectal Gyrus</td>
</tr>
<tr>
<td></td>
<td>-3  51  -9</td>
<td>6.30</td>
<td></td>
<td>L Mid Orbital Gyrus</td>
</tr>
<tr>
<td></td>
<td>-12  36 -12</td>
<td>5.81</td>
<td></td>
<td>L Mid Orbital Gyrus</td>
</tr>
<tr>
<td>Contrast</td>
<td>Coordinates (mm)</td>
<td>Peak (t)</td>
<td>Cluster (k)</td>
<td>Location</td>
</tr>
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<td>----------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>X</td>
<td>Y</td>
<td>Z</td>
<td></td>
</tr>
<tr>
<td>None-Pain</td>
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<td></td>
<td></td>
<td></td>
</tr>
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<td>(Cont)</td>
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<td>-51</td>
<td>45</td>
<td>6.14</td>
</tr>
<tr>
<td>-39 -78 36</td>
<td>6.08</td>
<td>20</td>
<td>L Middle Occipital Gyrus IPC (PGp)</td>
<td></td>
</tr>
<tr>
<td>-57 -12 -15</td>
<td>5.74</td>
<td>31</td>
<td>L Middle Temporal Gyrus</td>
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</tr>
<tr>
<td>None-Touch</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-45</td>
<td>-57</td>
<td>24</td>
<td>7.17</td>
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<td>54</td>
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<td>24</td>
<td>6.46</td>
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<td>-54</td>
<td>39</td>
<td>5.64</td>
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<td></td>
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<td>-75</td>
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<td>5.54</td>
</tr>
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<td></td>
<td>-3</td>
<td>51</td>
<td>-6</td>
<td>5.27</td>
</tr>
<tr>
<td></td>
<td>-24</td>
<td>27</td>
<td>36</td>
<td>5.23</td>
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<td></td>
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<td>-18</td>
<td>5.09</td>
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<tr>
<td></td>
<td>33</td>
<td>-84</td>
<td>27</td>
<td>4.92</td>
</tr>
</tbody>
</table>

*Note. Peaks are significant at p < .05 FWE. L = left, R = right, IPC = Inferior Parietal Cortex, ACC = Anterior Cingulate Cortex, MCC = Middle Cingulate Cortex; L = left; R = right. * indicates the label in brackets was obtained from the neurosynth.org website as opposed to Anatomy Toolbox or other atlas.*
Simple Effects of Pressure: Activations

Figure 6 Activations associated with pain, touch, and no pressure conditions, as determined by t-contrasts

Simple Effects of Pressure: Deactivations

Figure 7 Deactivations associated with pain and touch conditions, as determined by t-contrasts
Across both groups, there were significant activations for the contrast examining pain compared with touch. Activations during this contrast display areas with higher levels of activation for pain stimuli as compared with touch stimuli. Activated areas included: the left MCC/ACC, bilateral insula, bilateral cerebellum, brainstem (thalamus and mid-brainstem), the left SMA, right supramarginal gyrus, right precuneus, and areas of the left occipital gyrus. Areas that were not activated included the S1 and S2, as well as the thalamus. Deactivations were examined by comparing the touch condition to the pain condition, resulting in an image of areas that are more activated during touch than during painful pressure. There were no areas that were more active during touch than during painful stimuli.

When examining the contrast comparing pain with no pressure, which is a common means of looking at pain in the literature, areas of activation across groups included the left MCC/ACC, bilateral insula, left S2, bilateral SMA and precentral gyrus (BA6), bilateral precuneus, bilateral middle frontal gyrus, right inferior frontal gyrus, middle temporal gyrus, and several other areas of activation throughout the occipital cortex. Deactivations were examined by comparing the no pressure condition to the pain condition, resulting in an image of areas that are more activated during no pressure than during painful pressure. Deactivations were present bilaterally in the angular and middle temporal gyri. There were also deactivations in the right rectal gyrus, right precuneus, left middle orbitofrontal gyrus and left middle occipital gyrus.

Activations associated with touch, as opposed to pain, included the bilateral MCC/ACC, right insula, right thalamus, left S2, bilateral cerebellum, bilateral supramarginal gyrus, right inferior, superior, and middle frontal gyrus, right putamen and caudate, left SMA, left middle orbital gyrus, and bilateral middle temporal gyrus. Deactivations were present bilaterally in the angular gyrus and middle temporal gyrus, as well as in the right middle temporal gyrus, right middle occipital gyrus, left precuneus, and left middle frontal gyrus.
5.5.3. **Main Effect of Word**

There was no main effect of word (see Table 8), suggesting that the presentation of pain words and neutral words did not produce differing effects when collapsing across pressure values.

In order to examine whether there were differences in pain words and neutral words when there was no pressure being applied, this contrast was examined for both groups. There were no significant group differences; however, across both groups there were differences between the painful and neutral word conditions (Table 10).
Table 10

*Activations Associated With Painful Words (Generated by Contrasting Painful Words Minus Neutral Words) During No Pressure Application, p<.05, FWE.*

<table>
<thead>
<tr>
<th>Coordinates (mm)</th>
<th>Cluster Size (k)</th>
<th>Peak Z</th>
<th>Location</th>
<th>(Anatomy Toolbox)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Y</td>
<td>Z</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>0</td>
<td>3</td>
<td>51</td>
<td>6.64</td>
</tr>
<tr>
<td>-57</td>
<td>-27</td>
<td>27</td>
<td>151</td>
<td>6.27</td>
</tr>
<tr>
<td>-57</td>
<td>-27</td>
<td>45</td>
<td></td>
<td>5.87</td>
</tr>
<tr>
<td>-63</td>
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<td>5.39</td>
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<td>-3</td>
<td>3</td>
<td></td>
<td>5.42</td>
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<td>60</td>
<td>-15</td>
<td>18</td>
<td>13</td>
<td>5.47</td>
</tr>
<tr>
<td>15</td>
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<td>3</td>
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<td>-6</td>
<td>-18</td>
<td>-15</td>
<td>4</td>
<td>5.19</td>
</tr>
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<td>-36</td>
<td>45</td>
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</tr>
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<td>-99</td>
<td>-9</td>
<td>2</td>
<td>5.14</td>
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<td>9</td>
<td>-3</td>
<td>8</td>
<td>5.09</td>
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<td>-6</td>
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<td>5.07</td>
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<td>36</td>
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<td>3</td>
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<td>4.89</td>
</tr>
<tr>
<td>-6</td>
<td>-15</td>
<td>0</td>
<td>2</td>
<td>4.82</td>
</tr>
</tbody>
</table>

*Note.* L = left; R = right.
5.5.4. Interaction: Word x Pressure

There were no significant group interactions at the whole brain level; however across both groups, the left MCC ($p < .05$ FWE) and the left postcentral gyrus ($p = .07$ FWE) demonstrated a word by pressure interaction when a small volume correction (SVC) encompassing the pain matrix was applied (Table 11).

Table 11

*Peak Activation Results for the Interaction of Word and Pressure Using a Small Volume Correction, $p<.05$, FWE.*

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Coordinates (mm)</th>
<th>Peak (F)</th>
<th>Cluster Size (k)</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Word x Pressure</td>
<td>-3  -39  51</td>
<td>16.06</td>
<td>76</td>
<td>L MCC</td>
</tr>
<tr>
<td>(SVC pain matrix)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-27  -39  63</td>
<td>12.59</td>
<td>14</td>
<td>L Postcentral Gyrus - Area 1/2/3b</td>
</tr>
</tbody>
</table>

*Note.* MCC = Middle Cingulate Cortex; L = left.

Plots were generated to examine the interactions that occurred within the peak points of the pain matrix (see Figure 8). In the MCC and S1, neutral words resulted in greater activation than pain words for the painful pressure condition; however, pain words resulted in greater activation than neutral words for the no pressure condition. There were no significant differences between words for the touch condition. In the MCC, touch had significantly lower activations than none; there were no significant differences between pain and touch or pain and none. It is surmised that these findings are due to the high activations present for the no pressure, painful word condition. In S1, pain pressure resulted in greater activation than touch pressure, which showed greater activations than no pressure.
Figure 8. Interaction of pressure by word. \((p < .05, \text{FWE})\) without a small volume correction. The colour scale represents F-values, which begin with the critical F-value associated with a \((p < .05, \text{FWE})\) cut-off \((F = 14.35)\). On the depiction of the brain, the colours toward the red end of the spectrum indicate higher F scores (e.g., higher magnitudes of activation). Graphs depict parameter estimates for each of the study conditions in the left MCC and the left postcentral gyrus.
5.5.5. Interaction: Group x Pressure

It was predicted, *a priori*, that the difference scores in activation between pain conditions and touch conditions would be smaller for the PVD group in all areas of the pain matrix due to many of the touch trials potentially being perceived as painful for the PVD group, particularly when pain words were compared with touch. As these were *a priori* hypotheses, a planned comparison between groups was conducted despite no findings of a main effect of group in areas of the pain matrix. Peak points within areas of the pain matrix were chosen from the significant activations associated with the main effect and simple effects of pressure. Difference scores were calculated for each participant by extracting the parameter estimates for the non-painful pressure conditions and subtracting them from the painful pressure conditions.

In the right S1 area (21, -42, 69), there were no significant group differences in the difference score between pain and touch; however, in the left S2 (-51, -24, 24), women with PVD had a smaller difference in magnitude of activation between pain and touch activations (*M* difference = .53) than did controls (*M* difference = .97), *p* < .05. There were no significant group differences in the magnitude of scores between pain and touch in any of the cognitive/affective regions of the brain (e.g., ACC).

5.6. Study #2

5.6.1. Psychosocial Variables

5.6.1.1. Anxiety

Examination of psychosocial variables between groups revealed significant group differences in trait anxiety, as measured by the STAI-T (*p* <.001); women with PVD reported greater levels of anxiety than control women (Table 12). There were no significant group differences in state anxiety, either at the interview, or immediately preceding the fMRI testing session. Anxiety was also measured by the PASS and the ASI, and no significant group differences were revealed. When vulvar pain of the PVD group was compared with worst regularly experienced pain of the control group, significant differences emerged on
the PVAQ, with women with PVD endorsing more pain vigilance than control women \((p < .01)\). Despite the large number of non-significant group differences, effect sizes for many of the measures reveal a medium effect size.

Women with PVD were asked to fill out the PASS and PVAQ twice: once with respect to their vulvar pain and once with respect to their worst regularly experienced non-vulvar pain. There were no differences within the PVD group in the non-vulvar or vulvar PASS or PVAQ scores.
Table 12

Means (M) and Standard Deviations (SD) Associated with Anxiety Variables

<table>
<thead>
<tr>
<th></th>
<th>PVD</th>
<th>Control</th>
<th>t</th>
<th>p</th>
<th>Effect size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STAI-T</td>
<td>47.40 (5.03)</td>
<td>36.80 (7.63)</td>
<td>-4.49</td>
<td>.000</td>
<td>1.64***</td>
</tr>
<tr>
<td>STAI-S</td>
<td>36.60 (12.45)</td>
<td>30.60 (9.94)</td>
<td>-1.46</td>
<td>.156</td>
<td>.53**</td>
</tr>
<tr>
<td>STAI-S (fMRI)</td>
<td>29.73 (8.28)</td>
<td>28.80 (5.98)</td>
<td>-0.35</td>
<td>.730</td>
<td>.13</td>
</tr>
<tr>
<td>PVAQ</td>
<td>39.64 (18.15)</td>
<td>29.21 (20.57)</td>
<td>-1.45</td>
<td>.159</td>
<td>.54**</td>
</tr>
<tr>
<td>PVAQ(v)</td>
<td>48.67 (16.23)</td>
<td>29.21 (20.57)</td>
<td>-2.84</td>
<td>.009</td>
<td>1.05***</td>
</tr>
<tr>
<td>PASS fear</td>
<td>5.40 (5.79)</td>
<td>5.07 (5.66)</td>
<td>0.02</td>
<td>.88</td>
<td>.06</td>
</tr>
<tr>
<td>PASS avoid</td>
<td>11.07 (6.97)</td>
<td>7.71 (5.31)</td>
<td>2.10</td>
<td>.16</td>
<td>.54**</td>
</tr>
<tr>
<td>PASS physiological</td>
<td>6.20 (4.78)</td>
<td>5.08 (6.08)</td>
<td>0.31</td>
<td>.585</td>
<td>.20*</td>
</tr>
<tr>
<td>PASS cognitive</td>
<td>13.40 (8.30)</td>
<td>9.00 (7.30)</td>
<td>2.29</td>
<td>.142</td>
<td>.56**</td>
</tr>
<tr>
<td>PASS total</td>
<td>36.07 (21.51)</td>
<td>26.87 (22.99)</td>
<td>1.46</td>
<td>.238</td>
<td>.41*</td>
</tr>
<tr>
<td>PASS(v) fear</td>
<td>4.73 (3.86)</td>
<td>5.07 (5.66)</td>
<td>0.04</td>
<td>.852</td>
<td>.07</td>
</tr>
<tr>
<td>PASS(v) avoid</td>
<td>7.53 (4.76)</td>
<td>7.71 (5.31)</td>
<td>0.01</td>
<td>.924</td>
<td>.04</td>
</tr>
<tr>
<td>PASS(v) physiological</td>
<td>6.13 (5.41)</td>
<td>5.08 (6.08)</td>
<td>0.24</td>
<td>.626</td>
<td>.18</td>
</tr>
<tr>
<td>PASS(v) cognitive</td>
<td>12.47 (7.29)</td>
<td>9.00 (7.30)</td>
<td>1.64</td>
<td>.212</td>
<td>.48*</td>
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<td>PASS(v) total</td>
<td>30.87 (17.20)</td>
<td>26.87 (22.99)</td>
<td>0.51</td>
<td>.482</td>
<td>.20*</td>
</tr>
<tr>
<td>ASI physical</td>
<td>3.97 (6.00)</td>
<td>5.46 (5.28)</td>
<td>0.50</td>
<td>.485</td>
<td>.26*</td>
</tr>
<tr>
<td>ASI cognitive</td>
<td>5.60 (6.56)</td>
<td>3.50 (3.74)</td>
<td>1.10</td>
<td>.303</td>
<td>.39*</td>
</tr>
<tr>
<td>ASI social</td>
<td>9.52 (6.33)</td>
<td>7.48 (4.68)</td>
<td>0.96</td>
<td>.335</td>
<td>.37*</td>
</tr>
<tr>
<td>ASI total</td>
<td>19.09 (17.21)</td>
<td>16.45 (12.80)</td>
<td>0.14</td>
<td>.713</td>
<td>.17</td>
</tr>
</tbody>
</table>

Note. (v) = vulvar pain; * = small effect (0.2); ** = medium effect (0.5); *** = large effect (0.8; Cohen, 1988). For correlations amongst the anxiety measures, see Appendix R.
5.6.1.2. Catastrophizing

Catastrophizing was measured by the PCS (Table 13). Women with PVD filled out each of these scales twice, once with respect to their vulvar pain, and once with respect to their worst regularly experienced non-vulvar pain; control women filled them out regarding their worst non-vulvar pain. Worst regularly experienced non-vulvar pains endorsed by both groups included: menstrual pain (control = 4; PVD = 2), yeast infections and urinary tract infections (control = 3; PVD = 1), headaches/migraines (control = 2; PVD = 4), stomach problems (control = 1; PVD = 1), back and neck pain (control = 1; PVD = 3), breast and chest pain (control = 1; PVD = 1). Additional pains reported by control women included heal spur (n = 1) and anal pain (n = 1). Additional pains reported by women with PVD included gall bladder (n = 1) and leg pain (n = 1). There were no significant group differences in pain intensity for worst non-vulvar pain (control \( M = 5.21, SD = 2.72; PVD M = 6.13, SD = 2.42), t(26) = -0.96, ns\).

Women with PVD reported greater catastrophizing than controls with respect to both their vulvar \( p < .01 \) and non-vulvar \( p < .05 \) pain as measured by the PCS. In both cases, women with PVD were above the cut-off for chronic pain populations, which is a score of 30 out of a possible score of 0 to 52 (Sullivan et al., 1995). When examining individual scores, 9/14 women with PVD (64%) scored above the chronic pain cut-off, whereas only 4/14 women (29%) scored above the chronic pain cut-off. There were no significant differences in pain ratings between vulvar pain \( (M = 5.93, SD = 1.91) \) and worst regularly experienced non-vulvar pain \( (M = 6.13, SD = 2.42) \) when comparing PCS non-vulvar pain to PCS vulvar pain in women with PVD.
Table 13

Means (M) and Standard Deviations (SD) Associated with Catastrophizing Variables

<table>
<thead>
<tr>
<th></th>
<th>PVD</th>
<th>Control</th>
<th>F</th>
<th>p</th>
<th>Effect size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS rumination</td>
<td>12.00 (4.34)</td>
<td>7.87 (4.02)</td>
<td>7.32</td>
<td>.011</td>
<td>.99***</td>
</tr>
<tr>
<td>PCS magnification</td>
<td>6.20 (3.41)</td>
<td>4.89 (1.96)</td>
<td>1.73</td>
<td>.199</td>
<td>.47*</td>
</tr>
<tr>
<td>PCS helplessness</td>
<td>14.40 (7.48)</td>
<td>8.60 (2.87)</td>
<td>7.86</td>
<td>.009</td>
<td>1.02***</td>
</tr>
<tr>
<td>PCS total</td>
<td>32.60 (14.37)</td>
<td>21.33 (8.36)</td>
<td>4.87</td>
<td>.036</td>
<td>.96***</td>
</tr>
<tr>
<td>PCS(v) rumination</td>
<td>11.47 (4.31)</td>
<td>7.87 (4.02)</td>
<td>5.61</td>
<td>.025</td>
<td>.86***</td>
</tr>
<tr>
<td>PCS(v) magnification</td>
<td>5.60 (2.41)</td>
<td>4.87 (1.96)</td>
<td>0.83</td>
<td>.370</td>
<td>.36*</td>
</tr>
<tr>
<td>PCS(v) helplessness</td>
<td>15.4 (5.93)</td>
<td>8.60 (2.87)</td>
<td>15.99</td>
<td>.000</td>
<td>1.46***</td>
</tr>
<tr>
<td>PCS(v) total</td>
<td>32.47 (11.69)</td>
<td>21.33 (8.36)</td>
<td>6.91</td>
<td>.014</td>
<td>1.10***</td>
</tr>
</tbody>
</table>

*Note. (v) = vulvar pain; * = small effect (0.2); *** = large effect (0.8; Cohen, 1988).

5.6.1.3. Correlations between Neuroimaging & Psychosocial Variables

Anxiety. Possible scores on the STAI-T range from 20 to 80, with higher scores representing greater levels of anxiety. Trait anxiety scores in the control group ranged from 20 to 49 with a mean score of 36.80 (SD = 7.63), placing this group in the low anxiety range on the STAI-T. Scores in the PVD group ranged from 26 to 63 with a mean score of 47.40 (SD = 5.03), placing this group in the moderate anxiety range on the STAI-T. Trait anxiety was examined as a covariate with painful stimuli (Table 14). Both groups showed activation associated with a significant positive correlation in the right middle frontal gyrus, meaning that, higher levels of trait anxiety are associated with increased brain activation. Control women showed an increase in activity in the left superior medial gyrus in association with anxiety and a decrease in activity in the right middle temporal gyrus as anxiety increased, which was not demonstrated by women with PVD.
Table 14

*Correlations between Trait Anxiety (STAI-T) and Neural Activations During Pain*

<table>
<thead>
<tr>
<th>Coordinates (mm)</th>
<th>Peak (t)</th>
<th>Cluster size (k)</th>
<th>Z</th>
<th>Label (Anatomy Toolbox)</th>
<th>Total r</th>
<th>Control r</th>
<th>PVD r</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Y</td>
<td>Z</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>33</td>
<td>-6</td>
<td>4.21</td>
<td>6</td>
<td>3.61</td>
<td>R Middle Frontal Gyrus</td>
<td>.55**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coordinates (mm)</th>
<th>Peak (F)</th>
<th>Cluster size (k)</th>
<th>Z</th>
<th>Label (Anatomy Toolbox)</th>
<th>Total r</th>
<th>Control r</th>
<th>PVD r</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Y</td>
<td>Z</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>-9</td>
<td>-21</td>
<td>16.54</td>
<td>4</td>
<td>3.32</td>
<td>R Middle Temporal Gyrus</td>
<td>-.04</td>
</tr>
<tr>
<td>51</td>
<td>-54</td>
<td>27</td>
<td>15.13</td>
<td>2</td>
<td>3.20</td>
<td>R Angular Gyrus (IPC PGa)</td>
<td>.06</td>
</tr>
</tbody>
</table>

*Note.* *p ≤ .05, **p < .01, ***p < .001. Peaks represent areas of significance in a correlation map between STAI-T scores and pain-evoked activity across both groups. R values were generated by correlating the parameter estimates of the peak points of the correlation map with the STAI-T scores for each subject in order to assess whether a significant contrast was being driven by the PVD group or the control group.
PVD and control groups were combined and split into those who scored in the moderate range or above on the STAI-T and those who scored in the low range. Eight women with PVD and 6 control women scored in the moderate or high ranges. High and low groups were compared in a t-test with STAI-T entered as a covariate to examine areas of brain activation related to level of catastrophizing. There was no significant difference in pressure pain threshold between high and low anxiety groups (high M = 50.61, SD = 61.29; low M = 51.33; SD = 47.26) or in pressure applied to generate a pain intensity rating of 4/10 (high M = 177.11, SD = 116.46; low M = 235.25, SD = 172.40). Those high on anxiety had significantly greater activation in the ACC than the low anxiety group (Table 15). The low anxiety group did not have significantly greater neural activation in any regions as compared to the high anxiety group.

Table 15

Neural Activations Associated with High and Low Levels of Trait Anxiety

<table>
<thead>
<tr>
<th>Coordinates (mm)</th>
<th>Peak (t)</th>
<th>Cluster Size (k)</th>
<th>Location (Anatomy Toolbox)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X Y Z (mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High &gt; Low</td>
<td>-9 -51 27</td>
<td>4.65</td>
<td>21</td>
</tr>
<tr>
<td>-9 -48 27</td>
<td>3.95</td>
<td>6</td>
<td>3.43</td>
</tr>
<tr>
<td>Low &gt; High</td>
<td>- - -</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note. L = left; R = right. N = 28.

Pain Vigilance Awareness. Control women’s scores ranged from 5-67 out of a possible 0-80, with a mean of 29.21 (SD = 20.57). Women with PVD had scores that ranged from 17-69, with a mean of 48.67 (SD = 16.23). The peaks presented in Table 16 are from the pain-none contrast with PVAQ(vulvar) entered as a covariate. Both groups showed positive correlations between PVAQ scores and brain activity in the left middle frontal gyrus and many areas of the left PFC. Brain activation in the right angular gyrus was negatively associated with PVAQ scores for both groups. Women with PVD showed positive correlations bilaterally throughout the PFC (with the exception of the left superior frontal gyrus, where...
there was a significant negative correlation). Women with PVD also had positive correlations in the right precentral gyrus and middle occipital cortex.
Table 16

**Correlations between Pain Vigilance (PVAQ) and Neural Activations During Pain**

### Overall Group Activations Associated with Positive Correlations

<table>
<thead>
<tr>
<th>Coordinates (mm)</th>
<th>Peak (t)</th>
<th>Cluster Size (k)</th>
<th>Z</th>
<th>Label (Anatomy Toolbox)</th>
<th>Total r</th>
<th>Control r</th>
<th>PVD r</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 39 0</td>
<td>5.98</td>
<td>72</td>
<td>4.63</td>
<td>R Middle Frontal Gyrus</td>
<td>0.69**</td>
<td>0.46</td>
<td>0.87***</td>
</tr>
<tr>
<td>12 30 -12</td>
<td>4.43</td>
<td></td>
<td>3.75</td>
<td>R Superior Frontal Gyrus</td>
<td>0.63**</td>
<td>0.36</td>
<td>0.79**</td>
</tr>
<tr>
<td>-15 36 -15</td>
<td>5.37</td>
<td>17</td>
<td>4.31</td>
<td>L Superior Orbital Gyrus</td>
<td>0.64**</td>
<td>0.72**</td>
<td>0.76**</td>
</tr>
<tr>
<td>-21 15 33</td>
<td>4.09</td>
<td>2</td>
<td>3.53</td>
<td>L Middle Frontal Gyrus</td>
<td>0.69**</td>
<td>0.61*</td>
<td>0.66*</td>
</tr>
<tr>
<td>-42 -27 -15</td>
<td>3.72</td>
<td>2</td>
<td>3.27</td>
<td>L Inferior Temporal Gyrus</td>
<td>0.58**</td>
<td>0.51*</td>
<td>0.66*</td>
</tr>
</tbody>
</table>

### Overall Group Activations Associated with Negative Correlations

<table>
<thead>
<tr>
<th>Coordinates (mm)</th>
<th>Peak (t)</th>
<th>Cluster Size (k)</th>
<th>Z</th>
<th>Label (Anatomy Toolbox)</th>
<th>Total r</th>
<th>Control r</th>
<th>PVD r</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 30 51</td>
<td>5.17</td>
<td>25</td>
<td>4.20</td>
<td>L Superior Frontal Gyrus</td>
<td>-0.59**</td>
<td>-0.73**</td>
<td>-0.73**</td>
</tr>
<tr>
<td>48 -63 45</td>
<td>4.09</td>
<td>12</td>
<td>3.53</td>
<td>R Angular Gyrus</td>
<td>-0.55**</td>
<td>-0.63*</td>
<td>-0.65*</td>
</tr>
</tbody>
</table>
### Areas Of Correlation Map Where Groups Differ in Direction of Correlation

<table>
<thead>
<tr>
<th>Coordinates (mm)</th>
<th>Peak (F)</th>
<th>Cluster</th>
<th>Z</th>
<th>Label (Anatomy Toolbox)</th>
<th>Total r</th>
<th>Control r</th>
<th>PVD r</th>
</tr>
</thead>
<tbody>
<tr>
<td>X    Y    Z</td>
<td>Size (k)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48   -69  -12</td>
<td>18.18</td>
<td>6</td>
<td>3.46</td>
<td>R Middle Temporal Gyrus</td>
<td>0.04</td>
<td>-0.79**</td>
<td>0.62*</td>
</tr>
<tr>
<td>21   33    9</td>
<td>15.38</td>
<td>2</td>
<td>3.22</td>
<td>R Middle Frontal Gyrus</td>
<td>0.40</td>
<td>-0.18</td>
<td>0.78**</td>
</tr>
<tr>
<td>-18  42    15</td>
<td>14.90</td>
<td>3</td>
<td>3.17</td>
<td>L Middle Frontal Gyrus</td>
<td>0.33</td>
<td>-0.45</td>
<td>0.72**</td>
</tr>
<tr>
<td>-36  -6    27</td>
<td>3.82</td>
<td>3</td>
<td>3.34</td>
<td>L Precentral Gyrus</td>
<td>0.30</td>
<td>-0.30</td>
<td>0.69*</td>
</tr>
</tbody>
</table>

*Note. ^p = .08, *p ≤ .05, **p < .01, ***p < .001. Peaks represent areas of significance in a correlation map between PVAQ(v) scores and pain-evoked activity across both groups. R values were generated by correlating the parameter estimates of the peak points of the correlation map with the PVAQ(v) scores for each subject in order to assess whether a significant contrast was being driven by the PVD group or the control group.*
The PVAQ scores were split into high versus low groups using a median split, as the measure has no validated cut off score for high versus low or for chronic pain. Those who scored below the median (40.5) were classified as low scorers \((n = 14)\), and those who scored above this cut-off were classified as high scorers \((n = 14)\). Correlations between the PVAQ scores and neural activation during pain are reported in Table 17.

**Table 17**

**Neural Activations Associated with High and Low Levels of Pain-Related Anxiety**

<table>
<thead>
<tr>
<th>Coordinates (mm)</th>
<th>Peak Cluster</th>
<th>Z</th>
<th>Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>X Y Z (t)</td>
<td>Size (k)</td>
<td>(Anatomy Toolbox)</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------</td>
<td>---</td>
<td>-------</td>
</tr>
<tr>
<td>High &gt; Low</td>
<td>15 -30 -18</td>
<td>4.64</td>
<td>6</td>
</tr>
<tr>
<td>Low &gt; High</td>
<td>- - -</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Note.* R = right. N = 28.

**Catastrophizing.** Control women had an average score of 21.33 (SD = 8.36) with a range from 13-39 on the PCS of a possible range from 0-52. Women with PVD had an average score of 32.47 \((SD = 11.69)\) with a range from 17-54. The PCS, comparing PVD vulvar pain with controls worst pain, revealed significant overlapping correlations in areas of the prefrontal gyrus. Activation in the bilateral temporal gyrus, left insula, left amygdala, and right caudate was only significantly positively correlated with catastrophizing for control women. There were also many areas of the PFC that were negatively correlated with catastrophizing among control women, including bilateral precentral gyrus. Both groups showed positive and negative correlations in the superior frontal gyrus. Results are summarized in Table 18. In addition, there were significant correlations in the basal ganglia (putamen and caudate for control women and putamen for PVD women); however, the activations were at the level of single voxels, limiting any firm conclusions from being drawn.
Table 18

*Correlations between Catastrophizing (PCS) and Neural Activations During Pain*

**Overall Group Activations Associated with Positive Correlations**

<table>
<thead>
<tr>
<th>Coordinates (mm)</th>
<th>Peak (t)</th>
<th>Cluster Size (k)</th>
<th>Z</th>
<th>Label (Anatomy Toolbox)</th>
<th>Total r</th>
<th>Control r</th>
<th>PVD r</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Y</td>
<td>Z</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>48</td>
<td>24</td>
<td>4.45</td>
<td>10</td>
<td>3.76</td>
<td>R Middle Frontal Gyrus</td>
<td>.47*</td>
</tr>
<tr>
<td>57</td>
<td>-66</td>
<td>12</td>
<td>4.39</td>
<td>28</td>
<td>3.72</td>
<td>R Middle Temporal Gyrus (IPC PGp)</td>
<td>.47*</td>
</tr>
<tr>
<td>27</td>
<td>36</td>
<td>0</td>
<td>4.39</td>
<td>7</td>
<td>3.72</td>
<td>R Inferior Frontal Gyrus</td>
<td>.68***</td>
</tr>
<tr>
<td>-30</td>
<td>-3</td>
<td>-15</td>
<td>4.05</td>
<td>5</td>
<td>3.50</td>
<td>L Amygdala (LB)</td>
<td>.47*</td>
</tr>
<tr>
<td>-39</td>
<td>6</td>
<td>-6</td>
<td>3.76</td>
<td>8</td>
<td>3.30</td>
<td>L Insula</td>
<td>.37*</td>
</tr>
<tr>
<td>51</td>
<td>-51</td>
<td>12</td>
<td>3.70</td>
<td>2</td>
<td>3.26</td>
<td>R Middle Temporal Gyrus</td>
<td>.42*</td>
</tr>
</tbody>
</table>

**Overall Group Activations Associated with Negative Correlations**

<table>
<thead>
<tr>
<th>Coordinates (mm)</th>
<th>Peak (t)</th>
<th>Cluster Size (k)</th>
<th>Z</th>
<th>Label (Anatomy Toolbox)</th>
<th>Total r</th>
<th>Control r</th>
<th>PVD r</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Y</td>
<td>Z</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>-48</td>
<td>42</td>
<td>3.68</td>
<td>3</td>
<td>3.24</td>
<td>R Angular Gyrus</td>
<td>-.47*</td>
</tr>
<tr>
<td>21</td>
<td>63</td>
<td>-3</td>
<td>3.68</td>
<td>2</td>
<td>3.24</td>
<td>R Middle Frontal Gyrus</td>
<td>-.32</td>
</tr>
<tr>
<td>-3</td>
<td>24</td>
<td>54</td>
<td>3.57</td>
<td>2</td>
<td>3.17</td>
<td>L Superior Frontal Gyrus</td>
<td>-.34</td>
</tr>
<tr>
<td>42</td>
<td>36</td>
<td>15</td>
<td>3.49</td>
<td>2</td>
<td>3.11</td>
<td>R Inferior Frontal Gyrus</td>
<td>-.36</td>
</tr>
</tbody>
</table>
Areas Of Correlation Map Where Groups Differ in Direction of Correlation

<table>
<thead>
<tr>
<th>Coordinates (mm)</th>
<th>Peak (F)</th>
<th>Cluster</th>
<th>Z</th>
<th>Label (Anatomy Toolbox)</th>
<th>Total r</th>
<th>Control r</th>
<th>PVD r</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Y</td>
<td>Z</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>33.60</td>
<td>26</td>
<td>4.39</td>
<td>R Superior Frontal Gyrus</td>
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</tr>
<tr>
<td>24</td>
<td>60</td>
<td>-3</td>
<td>24.13</td>
<td>16</td>
<td>3.88</td>
<td>R Superior Orbital Gyrus</td>
<td>-.03</td>
</tr>
<tr>
<td>15</td>
<td>60</td>
<td>0</td>
<td>19.63</td>
<td></td>
<td>3.57</td>
<td>Orbital Gyrus</td>
<td>-.11</td>
</tr>
<tr>
<td>-33</td>
<td>-6</td>
<td>66</td>
<td>20.44</td>
<td>3</td>
<td>3.63</td>
<td>L Precentral Gyrus</td>
<td>-.29</td>
</tr>
<tr>
<td>-27</td>
<td>33</td>
<td>-15</td>
<td>15.63</td>
<td>3</td>
<td>3.24</td>
<td>L Inferior Frontal Gyrus (P.Orbitalis)</td>
<td>.13</td>
</tr>
<tr>
<td>48</td>
<td>9</td>
<td>48</td>
<td>15.04</td>
<td>3</td>
<td>3.19</td>
<td>R Precentral Gyrus</td>
<td>-.16</td>
</tr>
<tr>
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<td>27</td>
<td>30</td>
<td>3.71</td>
<td>3</td>
<td>3.27</td>
<td>L Superior Frontal Gyrus</td>
<td>.28</td>
</tr>
</tbody>
</table>

Note. ^ p = .08, * p ≤ .05, **p < .01, ***p < .001. Peaks represent areas of significance in a correlation map between PCS(v) scores and pain-evoked activity across both groups. R values were generated by correlating the parameter estimates of the peak points of the correlation map with the PCS(v) scores for each subject in order to assess whether a significant contrast was being driven by the PVD group or the control group.
PVD and control groups were combined and split into those who scored above the chronic pain cut off score on the PCS (30; Sullivan et al., 1995) and those who scored below. Nine women with PVD and 4 control women scored above the cut-off. High and low catastrophizers were compared in a t-test with PCS entered as a covariate to examine areas of brain activation related to level of catastrophizing (Table 19). There was no significant difference in pressure pain threshold between high and low catastrophizers (high $M = 33.31$, $SD = 29.28$; low $M = 66.33$, $SD = 64.63$) or in pressure applied to generate a pain intensity rating of 4/10 (high $M = 161.15$, $SD = 135.31$; low $M = 235.29$, $SD = 167.94$).

Table 19

<p>| Neural Activations Associated with High and Low Levels of Catastrophizing |
|-----------------------------|--------|--------|---------------|--------------------------|</p>
<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Peak (t)</th>
<th>Cluster Size (k)</th>
<th>Location (Anatomy Toolbox)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>45</td>
<td>18</td>
<td>3.97</td>
<td>6</td>
<td>R Middle Frontal Gyrus</td>
</tr>
<tr>
<td>-15</td>
<td>3</td>
<td>69</td>
<td>3.88</td>
<td>2</td>
<td>L Superior Frontal Gyrus</td>
</tr>
<tr>
<td>-21</td>
<td>9</td>
<td>-9</td>
<td>3.74</td>
<td>2</td>
<td>L Putamen</td>
</tr>
<tr>
<td>18</td>
<td>33</td>
<td>33</td>
<td>3.72</td>
<td>2</td>
<td>L Superior Frontal Gyrus</td>
</tr>
<tr>
<td>-57</td>
<td>3</td>
<td>-12</td>
<td>3.64</td>
<td>2</td>
<td>L Superior Temporal Gyrus</td>
</tr>
<tr>
<td>-3</td>
<td>-45</td>
<td>30</td>
<td>3.61</td>
<td>3</td>
<td>L Cingulate Gyrus</td>
</tr>
<tr>
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<td>12</td>
<td>-9</td>
<td>3.60</td>
<td>2</td>
<td>R Putamen</td>
</tr>
</tbody>
</table>

Further analyses were run at the whole group level ($N = 28$) to examine whether catastrophizing and pain-related anxiety displayed activations while controlling for the presence of the other variable. When catastrophizing (PCS) and pain-related anxiety (PVAQ) were both entered into SPM8 to examine the activations associated with these variables during pain, significant activations were present in areas of the PFC. The analyses that were run examined brain activations during pain and catastrophizing while
controlling for anxiety, and subsequently activations during pain and anxiety, while controlling for catastrophizing. Findings suggest that both variables play a role in the modulation of pain stimuli (Tables 20 & 21).

Table 20

Associations between Neural Activations with Two Covariates to Assess for the Independent Roles of Catastrophizing Controlling for Anxiety During Painful Stimulation at the Vulva.

<table>
<thead>
<tr>
<th>Coordinates (mm)</th>
<th>Peak (t)</th>
<th>Cluster size (k)</th>
<th>Z Location</th>
<th>Location (Anatomy Toolbox)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activations for Catastrophizing (PCS) with Anxiety (PVAQ) as a covariate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 -63 9</td>
<td>4.51</td>
<td>19</td>
<td>3.75</td>
<td>R Middle Temporal Gyrus</td>
</tr>
<tr>
<td>-60 -9 -9</td>
<td>4.21</td>
<td>6</td>
<td>3.57</td>
<td>L Middle Temporal Gyrus</td>
</tr>
<tr>
<td>-30 0 -18</td>
<td>4.01</td>
<td>3</td>
<td>3.44</td>
<td>L Amygdala</td>
</tr>
<tr>
<td>-36 15 -9</td>
<td>3.92</td>
<td>5</td>
<td>3.37</td>
<td>L Insula</td>
</tr>
<tr>
<td>-36 6 -6</td>
<td>3.89</td>
<td>12</td>
<td>3.36</td>
<td>L Insula</td>
</tr>
<tr>
<td>69 -24 27</td>
<td>3.61</td>
<td>2</td>
<td>3.17</td>
<td>R Supramarginal Gyrus</td>
</tr>
</tbody>
</table>

Deactivations for Catastrophizing (PCS) with Anxiety (PVAQ) as a covariate

<table>
<thead>
<tr>
<th>Coordinates (mm)</th>
<th>Peak (t)</th>
<th>Cluster size (k)</th>
<th>Z Location</th>
<th>Location (Anatomy Toolbox)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-24 57 3</td>
<td>4.22</td>
<td>6</td>
<td>3.57</td>
<td>L Superior Frontal Gyrus</td>
</tr>
<tr>
<td>15 60 3</td>
<td>4.17</td>
<td>5</td>
<td>3.54</td>
<td>R Superior Frontal Gyrus</td>
</tr>
<tr>
<td>-18 45 15</td>
<td>3.98</td>
<td>2</td>
<td>3.41</td>
<td>L Middle Frontal Gyrus</td>
</tr>
<tr>
<td>9 63 9</td>
<td>3.66</td>
<td>2</td>
<td>3.20</td>
<td>R Superior Frontal Gyrus</td>
</tr>
</tbody>
</table>

*Note.* (p<.001) (N = 28).
Table 21

**Associations between Neural Activations with Two Covariates to Assess for the Independent Roles of Anxiety Controlling for Catastrophizing During Painful Stimulation at the Vulva.**

<table>
<thead>
<tr>
<th>Coordinates (mm)</th>
<th>Peak Cluster size</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Y</td>
<td>Z</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activations for Anxiety (PVAQ) with Catastrophizing (PCS) as a covariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 39 3</td>
<td>4.74</td>
<td>24</td>
</tr>
<tr>
<td>24 27 -6</td>
<td>3.69</td>
<td>3.22</td>
</tr>
<tr>
<td>-18 45 15</td>
<td>4.52</td>
<td>9</td>
</tr>
<tr>
<td>-15 39 -9</td>
<td>4.52</td>
<td>13</td>
</tr>
<tr>
<td>21 24 24</td>
<td>3.63</td>
<td>2</td>
</tr>
<tr>
<td>Deactivations for Anxiety (PVAQ) with Catastrophizing (PCS) as a covariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 57 36</td>
<td>3.89</td>
<td>2</td>
</tr>
<tr>
<td>0 30 51</td>
<td>3.81</td>
<td>2</td>
</tr>
</tbody>
</table>

*Note.* (p<.001) (N = 28).

5.7. **Study #3**

Women with primary and secondary PVD were examined on demographic and sexual functioning variables (Table 22). Although these groups were not matched on any demographic variables, there were no statistically significant differences in age [Primary (M = 24.33, SD = 6.65); Secondary (M = 20.50, SD = 1.07), t(5.2) = 1.40, ns], parity [Primary = 17%; Secondary = 0%, t(5.0) = 1.00, ns], or hormonal contraceptive use [Primary = 50%; Secondary = 87.5%, t(8.1) = -1.46, ns]. For group differences in sexual and QST data see Table 21. Women with primary PVD had higher menstrual pain ratings, lower pressure pain thresholds (higher sensitivity), and less intercourse attempts per month than women with
secondary PVD. Women with primary PVD initiate intercourse less often (less than a quarter of the time as compared to almost 50% for women with secondary PVD). As compared to women with secondary PVD, primary women with PVD also have significantly less confidence participating in intercourse when their partner initiates, and a trend toward less confidence when they initiate.
Table 22

*Means (M), Standard Deviations (SD), and Percentages Associated with Pain Characteristics of Women with Primary and Secondary PVD*

<table>
<thead>
<tr>
<th></th>
<th>Primary PVD</th>
<th>Secondary PVD</th>
<th>t</th>
<th>p</th>
<th>Effect size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Age at first pain</td>
<td>17.50 (2.07)</td>
<td>18.75 (1.28)</td>
<td>1.30</td>
<td>.230</td>
<td>.73**</td>
</tr>
<tr>
<td>Pain duration (years)</td>
<td>6.83 (5.67)</td>
<td>1.75 (1.28)</td>
<td>-2.16</td>
<td>.080</td>
<td>1.24***</td>
</tr>
<tr>
<td>Menstrual pain (0-10)</td>
<td>3.67 (1.97)</td>
<td>1.50 (1.20)</td>
<td>2.57</td>
<td>.025</td>
<td>1.50***</td>
</tr>
<tr>
<td>Pressure pain threshold (grams)</td>
<td>13.83 (7.88)</td>
<td>33.13 (17.92)</td>
<td>2.45</td>
<td>.031</td>
<td>1.42***</td>
</tr>
<tr>
<td>Moderate pressure pain of 4/10 (grams)</td>
<td>147.08 (91.71)</td>
<td>128.91 (62.15)</td>
<td>0.44</td>
<td>.665</td>
<td>.23*</td>
</tr>
<tr>
<td>Pain with gynecological exam (0-10)</td>
<td>5.28 (2.04)</td>
<td>4.05 (1.13)</td>
<td>1.34</td>
<td>.221</td>
<td>.75**</td>
</tr>
<tr>
<td>Average intercourse pain (0-10)</td>
<td>6.50 (2.07)</td>
<td>5.25 (1.67)</td>
<td>1.25</td>
<td>.234</td>
<td>.66**</td>
</tr>
<tr>
<td>% of time intercourse is painful</td>
<td>84.17 (18.00)</td>
<td>82.50 (21.04)</td>
<td>-0.16</td>
<td>.879</td>
<td>.09</td>
</tr>
<tr>
<td>How long pain lasts after intercourse (hours)</td>
<td>4.86 (9.43)</td>
<td>0.26 (0.27)</td>
<td>-1.19</td>
<td>.188</td>
<td>.69**</td>
</tr>
<tr>
<td>Average number of intercourse attempts per month (past 6 months)</td>
<td>8.33 (6.28)</td>
<td>16.31 (6.83)</td>
<td>-2.24</td>
<td>.044</td>
<td>1.31***</td>
</tr>
<tr>
<td>% of time initiated by PVD woman</td>
<td>22.83 (22.09)</td>
<td>46.88 (16.24)</td>
<td>-2.36</td>
<td>.036</td>
<td>1.38***</td>
</tr>
<tr>
<td>Confidence engaging when self-initiated</td>
<td>5.40 (3.65)</td>
<td>9.20 (1.06)</td>
<td>-2.53</td>
<td>.009</td>
<td>1.48***</td>
</tr>
<tr>
<td>Confidence engaging when partner initiated</td>
<td>6.17 (2.48)</td>
<td>8.88 (1.81)</td>
<td>-2.37</td>
<td>.035</td>
<td>1.38***</td>
</tr>
<tr>
<td>% women who consulted a health professional</td>
<td>3 (50)</td>
<td>3 (37.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Number of health professionals</td>
<td>4.00 (3.46)</td>
<td>1.67 (0.58)</td>
<td>-1.15</td>
<td>.363</td>
<td>.94***</td>
</tr>
</tbody>
</table>
Women with primary and secondary PVD were also examined for group differences in the psychosocial measures (see Table 23). With respect to sexual functioning, women with primary PVD reported a trend toward lower levels of self-efficacy. Examination of the subscales of this measure revealed significantly lower sexual self-efficacy in the areas of eliciting/showing affection, communicating with partners, and body acceptance for women with primary PVD. These findings are consistent with earlier reported findings of decreased frequency initiating intercourse and lower confidence engaging in intercourse with a partner. With respect to sexual functioning, there were no significant group differences.
Table 23

*Means (M), Standard Deviations (SD), and Percentages Associated with Sexual Functioning and Sexual Self-Efficacy in Women with Primary and Secondary PVD*

<table>
<thead>
<tr>
<th></th>
<th>PVD Primary</th>
<th>PVD Secondary</th>
<th>F</th>
<th>p</th>
<th>Effect size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSFI desire</td>
<td>3.84(1.24)</td>
<td>3.75(0.77)</td>
<td>0.03</td>
<td>.874</td>
<td>.09</td>
</tr>
<tr>
<td>FSFI arousal</td>
<td>3.30(0.70)</td>
<td>4.13(1.21)</td>
<td>1.89</td>
<td>.197</td>
<td>.84***</td>
</tr>
<tr>
<td>FSFI lubrication</td>
<td>3.72(0.75)</td>
<td>4.09(1.21)</td>
<td>0.74</td>
<td>.409</td>
<td>.37*</td>
</tr>
<tr>
<td>FSFI orgasm</td>
<td>3.04(1.91)</td>
<td>4.10(2.01)</td>
<td>0.89</td>
<td>.367</td>
<td>.54**</td>
</tr>
<tr>
<td>FSFI satisfaction</td>
<td>3.52(1.25)</td>
<td>4.34(1.15)</td>
<td>1.49</td>
<td>.249</td>
<td>.68**</td>
</tr>
<tr>
<td>FSFI pain</td>
<td>2.64(0.67)</td>
<td>2.35(1.53)</td>
<td>0.16</td>
<td>.700</td>
<td>.25*</td>
</tr>
<tr>
<td>FSFI total</td>
<td>20.06(3.79)</td>
<td>22.76(5.22)</td>
<td>0.99</td>
<td>.341</td>
<td>.59**</td>
</tr>
<tr>
<td>SSES orgasm</td>
<td>5.65(2.55)</td>
<td>6.64(2.08)</td>
<td>0.64</td>
<td>.440</td>
<td>.83***</td>
</tr>
<tr>
<td>SSES desire</td>
<td>5.31(2.85)</td>
<td>7.56(2.04)</td>
<td>3.01</td>
<td>.108</td>
<td>.91***</td>
</tr>
<tr>
<td>SSES sensuality</td>
<td>7.36(2.99)</td>
<td>8.69(1.27)</td>
<td>1.29</td>
<td>.278</td>
<td>.58**</td>
</tr>
<tr>
<td>SSES arousal</td>
<td>5.13(3.33)</td>
<td>7.13(2.16)</td>
<td>1.87</td>
<td>.186</td>
<td>.71**</td>
</tr>
<tr>
<td>SSES affection</td>
<td>7.06(2.16)</td>
<td>9.17(1.21)</td>
<td>5.45</td>
<td>.038</td>
<td>1.22***</td>
</tr>
<tr>
<td>SSES communication</td>
<td>5.20(2.52)</td>
<td>8.25(1.66)</td>
<td>7.51</td>
<td>.018</td>
<td>1.43***</td>
</tr>
<tr>
<td>SSES body acceptance</td>
<td>4.42(2.76)</td>
<td>8.19(2.83)</td>
<td>6.21</td>
<td>.028</td>
<td>1.35***</td>
</tr>
<tr>
<td>SSES refusal</td>
<td>5.33(2.89)</td>
<td>6.19(3.13)</td>
<td>0.27</td>
<td>.611</td>
<td>.29*</td>
</tr>
<tr>
<td>SSES total</td>
<td>5.78(2.08)</td>
<td>7.66(1.30)</td>
<td>4.33</td>
<td>.060</td>
<td>1.08***</td>
</tr>
</tbody>
</table>

*Note. * = small effect (0.2); ** = medium effect (0.5); *** = large effect (0.8; Cohen, 1988).*
Women with primary PVD had higher state and trait anxiety than those with secondary PVD; however, there was no significant difference in their levels of anxiety immediately prior to participating in the fMRI and QST session. They also had higher anxiety sensitivity than women with secondary PVD and higher pain-related anxiety and pain vigilance. Examination of the subscales of the AS1 revealed higher levels of cognitive anxiety in women with primary PVD as compared to women with secondary PVD. With respect to pain vigilance, the primary PVD group displayed higher pain vigilance regarding non-vulvar pains, but there were no group differences for vulvar pain. On the PASS, women with primary PVD had higher levels of cognitive anxiety for their vulvar and non-vulvar pains, and higher levels of overall pain-anxiety and physiological arousal for their vulvar pain. Results are summarized in Table 24.
<table>
<thead>
<tr>
<th></th>
<th>PVD Primary M (SD)</th>
<th>PVD Secondary M (SD)</th>
<th>t</th>
<th>p</th>
<th>Effect size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAI-T</td>
<td>51.83 (8.47)</td>
<td>35.37 (10.38)</td>
<td>-3.17</td>
<td>.008</td>
<td>1.83***</td>
</tr>
<tr>
<td>STAI-S</td>
<td>44.50 (9.20)</td>
<td>29.00 (11.07)</td>
<td>-2.78</td>
<td>.017</td>
<td>1.61***</td>
</tr>
<tr>
<td>STAI-S (fMRI)</td>
<td>27.83 (4.75)</td>
<td>28.00 (4.81)</td>
<td>0.06</td>
<td>.950</td>
<td>.04</td>
</tr>
<tr>
<td>PVAQ</td>
<td>47.63 (11.96)</td>
<td>29.61 (15.39)</td>
<td>-2.37</td>
<td>.035</td>
<td>1.38***</td>
</tr>
<tr>
<td>PVAQ(v)</td>
<td>50.62 (17.36)</td>
<td>44.67 (15.19)</td>
<td>-0.68</td>
<td>.508</td>
<td>.40*</td>
</tr>
<tr>
<td>PASS fear</td>
<td>7.00 (6.39)</td>
<td>2.75 (2.92)</td>
<td>2.82</td>
<td>.119</td>
<td>.86***</td>
</tr>
<tr>
<td>PASS avoid</td>
<td>11.33 (6.38)</td>
<td>9.38 (6.67)</td>
<td>0.31</td>
<td>.590</td>
<td>.30*</td>
</tr>
<tr>
<td>PASS physiological</td>
<td>6.33 (3.88)</td>
<td>5.50 (5.58)</td>
<td>0.10</td>
<td>.760</td>
<td>.17</td>
</tr>
<tr>
<td>PASS cognitive</td>
<td>17.83 (7.49)</td>
<td>8.63 (5.95)</td>
<td>6.60</td>
<td>.025</td>
<td>1.36***</td>
</tr>
<tr>
<td>PASS total</td>
<td>42.50 (16.60)</td>
<td>26.25 (18.84)</td>
<td>2.81</td>
<td>.120</td>
<td>.92***</td>
</tr>
<tr>
<td>PASS(v) fear</td>
<td>5.57 (2.66)</td>
<td>3.50 (4.44)</td>
<td>1.11</td>
<td>.312</td>
<td>.57**</td>
</tr>
<tr>
<td>PASS(v) avoid</td>
<td>9.67 (4.97)</td>
<td>5.25 (3.69)</td>
<td>3.67</td>
<td>.080</td>
<td>1.01***</td>
</tr>
<tr>
<td>PASS(v) physiological</td>
<td>10.33 (5.61)</td>
<td>3.00 (3.12)</td>
<td>9.82</td>
<td>.009</td>
<td>1.61***</td>
</tr>
<tr>
<td>PASS(v) cognitive</td>
<td>16.00 (5.06)</td>
<td>8.25 (5.87)</td>
<td>6.68</td>
<td>.024</td>
<td>1.41***</td>
</tr>
<tr>
<td>PASS(v) total</td>
<td>41.67 (13.17)</td>
<td>20.00 (12.77)</td>
<td>9.61</td>
<td>.009</td>
<td>1.67***</td>
</tr>
<tr>
<td>ASI physical</td>
<td>7.50 (8.22)</td>
<td>1.82 (2.37)</td>
<td>3.52</td>
<td>.085</td>
<td>.94***</td>
</tr>
<tr>
<td>ASI cognitive</td>
<td>9.83 (8.26)</td>
<td>2.25 (2.96)</td>
<td>5.88</td>
<td>.032</td>
<td>1.22***</td>
</tr>
<tr>
<td>ASI social</td>
<td>13.00 (5.25)</td>
<td>7.36 (6.52)</td>
<td>2.99</td>
<td>.109</td>
<td>.95***</td>
</tr>
<tr>
<td>ASI total</td>
<td>30.33 (20.13)</td>
<td>11.43 (11.05)</td>
<td>5.11</td>
<td>.043</td>
<td>1.16***</td>
</tr>
</tbody>
</table>

**Note.** (v) = vulvar pain; * = small effect (0.2); ** = medium effect (0.5); *** = large effect (0.8; Cohen, 1988).
Women with primary PVD catastrophized more than those with secondary PVD about their vulvar and worst non-vulvar pains; however, when examining the subscales there was no difference in the amount of magnification for vulvar pain, suggesting that although they feel more helpless and they ruminate about their vulvar pain more often, they do not magnify it more than women with secondary PVD. This finding is consistent with a lack of group differences in reported pain vulvar pain ratings during intercourse and gynecological exams. There were also no group differences in the amount of rumination for non-vulvar pains, suggesting that women with primary PVD do not worry about and dwell on their non-vulvar pain issues more often than women with secondary PVD; however, they do magnify these pain issues, and they do feel more helpless with respect to these pains (Table 25).

Table 25

<table>
<thead>
<tr>
<th></th>
<th>PVD Primary</th>
<th>PVD Secondary</th>
<th>t</th>
<th>p</th>
<th>Effect size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCS(v) rum</td>
<td>14.83 (3.31)</td>
<td>9.00 (3.54)</td>
<td>9.80</td>
<td>.009</td>
<td>1.70***</td>
</tr>
<tr>
<td>PCS(v) mag</td>
<td>6.33 (1.97)</td>
<td>4.63 (2.39)</td>
<td>2.03</td>
<td>.18</td>
<td>.78**</td>
</tr>
<tr>
<td>PCS(v) help</td>
<td>19.50 (4.81)</td>
<td>12.13 (5.17)</td>
<td>7.40</td>
<td>.019</td>
<td>1.48***</td>
</tr>
<tr>
<td>PCS(v) total</td>
<td>40.67 (8.64)</td>
<td>25.75 (10.39)</td>
<td>8.11</td>
<td>.015</td>
<td>1.56***</td>
</tr>
<tr>
<td>PCS rum</td>
<td>13.17 (3.60)</td>
<td>10.13 (3.76)</td>
<td>2.33</td>
<td>.153</td>
<td>.83***</td>
</tr>
<tr>
<td>PCS mag</td>
<td>7.33 (2.58)</td>
<td>4.25 (1.39)</td>
<td>8.35</td>
<td>.014</td>
<td>1.49***</td>
</tr>
<tr>
<td>PCS help</td>
<td>17.83 (6.15)</td>
<td>9.88 (4.09)</td>
<td>8.52</td>
<td>.013</td>
<td>1.52***</td>
</tr>
<tr>
<td>PCS total</td>
<td>38.33 (10.75)</td>
<td>24.25 (8.51)</td>
<td>7.52</td>
<td>.018</td>
<td>1.45***</td>
</tr>
</tbody>
</table>

Note. * = small effect (0.2); ** = medium effect (0.5); *** = large effect (0.8; Cohen, 1988).
Brain activations and deactivations were examined for primary and secondary PVD. Duration of pain symptoms was entered into this analysis as a covariate, as previous research suggests that some of the differences between these two subtypes might be explained by the duration of pain (Goetsch, 2007). The following table (Table 25) depicts activations present in both groups for the pain-none contrast; however, this table is not representative of any statistically significant differences between groups, but rather an overview of active areas in the pain-none contrast for each group. For areas in which the groups differ from one another, refer to Table 26 below.
Table 26

*Areas of Activation and Deactivation for Women with PVD During Pain*

<table>
<thead>
<tr>
<th>Activations</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Cluster size (k)</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>L Putamen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>-21</td>
<td>3</td>
<td>-9</td>
<td>18</td>
<td>5.53</td>
</tr>
<tr>
<td>Secondary</td>
<td>-21</td>
<td>3</td>
<td>-9</td>
<td>66</td>
<td>5.50</td>
</tr>
<tr>
<td>R Putamen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>24</td>
<td>18</td>
<td>-3</td>
<td>36</td>
<td>5.73</td>
</tr>
<tr>
<td>Secondary</td>
<td>21</td>
<td>12</td>
<td>3</td>
<td>16</td>
<td>5.17</td>
</tr>
<tr>
<td>L Insula</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>-27</td>
<td>27</td>
<td>6</td>
<td>2</td>
<td>5.35</td>
</tr>
<tr>
<td>Secondary</td>
<td>-42</td>
<td>9</td>
<td>-6</td>
<td>16</td>
<td>5.34</td>
</tr>
<tr>
<td>R Insula</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>42</td>
<td>15</td>
<td>3</td>
<td>1</td>
<td>4.85</td>
</tr>
<tr>
<td>Secondary</td>
<td>39</td>
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</table>

*Note. p < .05, FWE; L = left, R = right.*
Women with primary PVD had higher levels of activation than women with secondary PVD in the left MCC, which is consistent with greater cognitive processing of pain stimuli for women with primary PVD. They also had higher levels of activation in the right putamen, the middle frontal gyrus and the middle occipital gyrus. See Table 27 for a summary of the results.

Table 27

Differences in Activation During Painful Stimulation Between Women with Primary and Secondary PVD

<table>
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<tr>
<th>Coordinates (mm)</th>
<th>Peak (t)</th>
<th>Cluster Size (k)</th>
<th>Location (Anatomy Toolbox)</th>
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Note. L = left; R = right.
Chapter 6. Discussion

6.1. General Overview

The purpose of the thesis was to examine the relationship among psychosocial, psychophysical, and neural functioning in women with PVD and healthy control women. In order to ensure that the current samples were consistent with samples already examined in the literature, a replication study of psychosocial and psychophysical characteristics was first conducted. Previous studies in the literature have consistently reported group differences in genital sensitivity to pressure pain, a finding that was replicated in the current study. Women with PVD exhibited significantly lower pressure pain thresholds and moderate pressure pain thresholds (pressure corresponding to a subjective intensity rating of 4/10) as compared to control participants. Group differences in sexual functioning were also examined. As hypothesized, women with PVD reported lower levels of sexual self-efficacy and sexual function as compared to healthy controls. The significant findings for sexual function, despite a small sample size, are indicative of just how strongly these variables are associated with PVD.

The first study aimed to examine the role of attention by presenting painful and non-painful words immediately prior to a randomized order of pressures (pain, touch, none). Findings of a main effect of pressure confirmed the hypothesis that, in many areas of the brain, pain results in greater activation than touch; however, for S1 and S2 areas, the painful and non-painful pressure conditions were not significantly different from one another, but both resulted in greater activation than the no pressure condition. Directed searches to examine word effects within the no pressure conditions revealed activation in the pain matrix for painful, but not neutral words, a finding that is consistent with the literature. The use of a small volume correction, using an image of the pain matrix generated from an amalgamation of activations in other pain studies (neurosynth.org), revealed an interaction between word and pressure in the MCC and postcentral gyrus (S1). Main effect group differences were only evident in the somatosensory cortex, likely reflecting the higher pressure levels used to generate a pain rating of
4/10 in the control group, as magnitude of S1 activity has been associated with the intensity of the actual
stimulus (Coghill et al., 1999). The lack of group differences throughout the pain matrix is consistent with
findings in the literature that, when controlling for subjective ratings, rather than applied levels of pain,
there are few differences in neural activation between chronic pain and healthy populations (e.g., Baliki et
al., 2010). Essentially, this finding can be reworded to state that, women with PVD show the same neural
activation patterns as healthy control women, even though the women with PVD are receiving
significantly lower pressure applications than the healthy control group for a pain rating of 4/10.

The second question aimed to investigate psychosocial functioning, and the correlations between
neural activation and anxiety and catastrophizing. Women with PVD reported higher levels of
catastrophizing when comparing their vulvar and worst regularly experienced non-vulvar pain with
control women’s reports of their worst regularly experienced pains. Women with PVD also reported
higher levels of trait anxiety, but not state anxiety when compared with control women. With respect to
pain-specific anxiety measures, women with PVD had significantly higher pain hypervigilance scores
when comparing their vulvar pain, but not non-vulvar pain, to control women. There were no significant
group differences in anxiety sensitivity or in vulvar or non-vulvar pain-related anxiety, as measured by
the PASS. It was suggested that small sample sizes may account for the lack of significant differences
compared with reports in the literature on psychosocial functioning in PVD, as studies of psychosocial
variables typically include far larger sample sizes. Calculation of effect sizes (Cohen’s d) revealed
moderate effect sizes on the non-vulvar PVAQ, avoidance and cognitive subscales of the non-vulvar
PASS, and state anxiety during the interview; however, effect sizes were small for anxiety sensitivity and
PASS total scores.

Women with PVD completed the anxiety and catastrophizing measures twice, once with respect
to their worst non-vulvar pain, and once for their vulvar pain. There were no significant differences
between these measures for non-vulvar and vulvar pain in the PVD group. This is likely reflective of a
generalized trend toward greater anxiety and catastrophizing, which is consistent with their higher scores
on trait anxiety compared with controls. Also, the regularly experienced pains included pains such as headaches and stomach pain, which are unprovoked, therefore perhaps resulting in higher scores because of their lack of predictability as compared with provoked vulvar pain.

An examination of the psychosocial correlates of neural activity during pain revealed that anxiety and catastrophizing were significantly correlated with neural activation during painful stimulation for both control women and women with PVD. Activations were present in areas of the PFC, and some medial, but no lateral pain processing areas, which is consistent with the hypothesis that, for all individuals, healthy or pain groups, psychosocial variables affect pain through the emotional and cognitive processing areas of the brain. Of note, catastrophizing was still correlated with areas of the PFC when controlling for pain-related anxiety, and pain-related anxiety was still correlated with areas of the PFC when controlling for catastrophizing. These findings suggest that both catastrophizing and pain-related anxiety play a unique role in pain processing.

The third question examined differences between primary and secondary PVD groups on psychophysical functioning, psychosocial functioning, and neural activations associated with painful stimuli. Women with primary and secondary PVD differed in psychophysical, psychosocial, and neural activation variables. Women with primary PVD had lower pain thresholds, higher levels of anxiety and pain catastrophizing, and greater magnitude of activations in emotional and cognitive pain areas. Despite these findings, they did not display significant differences in sexual functioning as measured by the FSFI. Perhaps the deficits in sexual functioning for women with primary and secondary PVD are associated with different causal or maintaining factors, and overall group differences between healthy control groups and PVD women on variables that have been explored to date are being driven by those women with primary PVD. It may also be the case that psychophysical and psychosocial dysfunction are not related to sexual functioning in a linear manner; despite group differences in levels of impairment in psychophysical and psychosocial functioning, the women in the secondary PVD group could feasibly still experience similar levels of sexual dysfunction to the primary PVD women. These findings suggest that although
there are similar sexual complaints and problems within the overall group, women with primary PVD are affected more significantly than women with secondary PVD outside a sexual context. Taken together, these findings support the emerging trend in the literature suggesting that women with primary and secondary PVD exhibit differences such that women with primary PVD seem to fare worse on several pain-related variables as compared with women with secondary PVD, but despite this, both groups experience similar problems with sexual functioning.

6.2. Defining the PVD Group

6.2.1. Psychophysical Testing

Consistent with previous research (Giesecke et al., 2004; Pukall et al., 2004), the current study found that, as compared to control participants, women with PVD exhibited significantly lower pressure pain thresholds at the vulvar vestibule as compared to control women. This finding indicates that women with PVD exhibit greater sensitivity to pressure stimuli; the first painful sensation experienced required less pressure in the PVD group than it did in the control group. Group differences also held true for the amount of pressure required to generate a moderate level of pain, which was conceptualized as a 4/10 on a pain intensity scale ranging from 0 (no pain) to 10 (worst pain imaginable), with women with PVD having a significantly lower moderate pressure pain threshold than control women.

6.2.2. Sexual Functioning

Consistent with previous research on vulvodynia, and despite the small sample size, significant differences were found between women with PVD and control women on a number of psychosocial and psychosexual variables. Consistent with a large body of independent research on psychosexual functioning, women with PVD report lower levels of sexual functioning in many domains as compared with controls (measured by the FSFI; Desrochers et al., 2009; Masheb et al., 2004; Rosen et al., 2010; Sutton et al., 2009). They also report lower sexual self-efficacy with respect to their desire levels, and they had a trend toward lower sexual self-efficacy with orgasm, a finding that is consistent with the
literature (Sutton et al., 2009). Although there was less perceived self-efficacy for orgasm, women with PVD did not report greater dysfunction in orgasm on the FSFI; however, there was a medium effect size (Cohen’s d), suggesting that they have some difficulty with orgasm as compared with control women. Reports of orgasm problems are variable in the literature, but a review paper found that women with PVD tend to report difficulty reaching orgasm (Desrochers et al., 2008).

6.3. **Study #1**

Whole group analyses (N = 28) revealed neural activations throughout the pain matrix, a finding that is consistent with previous studies in chronic pain patients, confirming that the fMRI data were modeled correctly.

6.3.1. **Main Effect of Group**

When a stimulus resulting in the same subjective pain rating amongst participants was applied, there was no robust main effect of group in areas of the pain matrix, which is consistent with findings from studies of a number of chronic pain conditions, including fibromyalgia (Burgmer et al, 2011; Cook et al., 2004; Giesecke et al., 2004; Gracely et al., 2002) and chronic low back pain (Baliki et al., 2010; Giesecke et al., 2004). In studies where pain intensity ratings were matched across groups, there are subtle, if any, group differences. In their chapter on pain imaging, Naylor and colleagues (2012) reported that findings of group differences between pain patients and healthy control participants are usually because the stimulus used was perceived as painful for the patient group, but not for the control group. In the current study, there was a main effect of group in the right precentral gyrus and the right temporal pole. Control women displayed greater activation than women with PVD in these areas.

For the precentral gyrus, the elevated response of control women makes sense, given that this area is believed to process the sensory aspect of pain, and in order to achieve a 4/10 pain rating, the control women were receiving increased pressures as compared with women with PVD. Increased activation for controls in a sensory processing area is consistent with previous findings comparing healthy
participants with chronic pain patients (Lanz et al., 2011). Lanz et al. (2011) surmise that stronger activation in healthy control participants may be the result of a higher level of baseline activity in patients, which may result in a decreased ability to detect measurable changes due to experimental stimuli. They further state that this elevated baseline might result from continuous noxious input to pain regions of the brain in patients with chronic pain or abnormal resting state activity in patients. There may also be some somatosensory deafferentation in chronic pain patients.

The finding of higher activations at the temporal pole for the control group, however, is not consistent with previous findings in the pain literature, though the small cluster size does merit cautious interpretation. For example, migraine patients had greater activation than healthy controls in this area (Moulton et al., 2011). Higher activations would be predicted to occur in women with PVD, as opposed to control women, because the temporal pole is an area that lies between the OFC and the amygdala, with connections to and from both regions (Olson, Plotzker, & Ezzyat, 2007). It is reported to be involved in the integration of pain processing, encoding and retrieval of emotional events (Dolan et al., 2000), the experience of pain-specific anxiety (Masaoka & Homma, 2000), and the processing of pain-related unpleasantness (Moulton et al., 2011). Women with PVD tend to have higher levels anxiety and higher unpleasantness ratings as compared with control participants (Pukall et al., 2005). This study did not examine unpleasantness ratings; however, unpleasantness ratings are typically (but not always) correlated with pain ratings in the pain literature (Price, 2000b), and have been correlated in previous studies examining PVD (e.g., Sutton, 2005). Although it would be inconsistent with the literature, perhaps due to the lengthy testing session, which is not standard for sensory testing experiments with this condition, the women with PVD felt more resigned to the pain, and the control women, who are not accustomed to vulvar pain, perceived it as more unpleasant. This is speculation and would require a study that examines unpleasantness. It remains unclear as to why control women had greater activation than PVD women in the temporal pole; however, the PVD group still displayed significant activation in this region, which is consistent with the tasks of integrating and processing the painful stimuli that were being administered.
6.3.2. Directed Search for Group by Pressure

An examination of the differences in activation strength between touch and pain revealed that women with PVD displayed a smaller difference score than control women in the left S2. This finding was expected, as it was hypothesized that the difference score would be of small magnitude for women with PVD due to augmented activation during touch (consistent with allostynia). A comparison of allostynia in neuropathic pain patients as compared to control individuals revealed significantly higher activations in S2 for the patients (Lanz et al., 2011). The current findings suggest that, when compared with control women, women with PVD may experience touch pressures as being more similar to painful pressures. These findings are consistent with a previous QST study, which found that control women perceived a touch sensation at levels of pressure that were already painful for women with PVD (Pukall et al., 2002), and provide further evidence of allostynia in women with PVD.

Contrary to the hypothesis, there were no group differences in the magnitude scores between pain and touch in cognitive/affective regions of the brain (e.g., ACC). It may be that difference scores between groups were similar because women with PVD have higher activations (though not significantly) for both touch and pain as compared with control women, thus the difference scores for the two groups are similar. This suggestion for explaining the findings fits with research demonstrating both allostynia and hyperalgesia in women with PVD (Pukall et al., 2002).

6.3.3. Main Effect of Word

There was no main effect of word in the factorial design at the whole brain level or using small volume corrections (SVCs). It was hypothesized that pain words would result in higher activations than neutral words in the medial (i.e. cognitive/emotional) pain areas. Previous studies (e.g., Eck et al., 2011; Richter et al., 2010) found differences in regions of the pain matrix during the processing of pain words as opposed to neutral words; however, these studies did not simultaneously apply a painful stimulus in their testing paradigms. In the present experiment, it is likely that, for conditions in which the word was
followed immediately by the application of a pressure stimulus, the effects might have been masked by the robust activation associated with the pressure stimulus. In other words, it was hypothesized that the activations associated with neutral and pain words did not differ enough in magnitude to result in differences that would augment the existing brain activation response to the applied pressures. As such, a t-test between painful and neutral words in the no pressure conditions was conducted. This exploration was permitted based on the a priori hypothesis that differences between pain words and neutral words might only exist for the no pressure conditions.

6.3.4. Directed Search of Word

Consistent with the literature, there were no brain areas in this contrast in which neutral words resulted in higher activation as compared with pain words. Also consistent with previous studies examining painful words (and painful visual primes), when no pain stimulus was applied, significant activations for pain words as compared to neutral words were found in areas of the pain matrix: including the insula, thalamus, S1 and S2 (Eck et al., 2011; Gu & Han, 2007; Osaka et al., 2004; Richter et al., 2010; Shimo et al., 2011). There were also activations in the ACC, consistent with findings from a previous study of increased activation in some areas of the ACC (Richter et al., 2010). Activations outside the pain matrix consisted of areas of the supramarginal gyrus, which are associated with language processing and reading. Other activated areas included parts of the basal ganglia (caudate and pallidum), and the MCC, all of which are associated with the experience of pain. The MCC has also been associated with sustained attention during a Stroop task (Peyron et al., 2000). Areas of the occipital lobe were also significantly more activated during the presentation of pain words. Similar areas have been activated during painful stimulation, with the conclusion that this activation may reflect a process of visual imagery associated with the painful stimuli (e.g., Baciu et al., 1999). The inferior frontal gyrus was activated, which is consistent with previous studies on single word reading (Price, 2000a). There was also activation in BA44, which is associated with semantic tasks, and similar areas have been reported as an area of
activation in other pain studies in patients with IBS (Drossman et al., 2003), fibromyalgia (Gracely et al., 2004), and PVD (Pukall et al., 2005). In some previous studies examining painful words, the cerebellum and putamen were activated (Eck et al., 2011; Osaka et al., 2004); however, these areas did not display significantly different activation between pain and neutral words in the present study. The lack of activation in this study is likely due to the experimental protocol. Both neutral and pain words were similarly activated because they were equally likely to be followed by a painful stimulus. Overall, the significant findings of differences in activation based on word presentation in the no pressure condition, but not the pain and touch conditions, are consistent with the hypothesis that the application of pressure activated the areas of the pain matrix regardless of word presentation, thus masking the expected main effect of word.

When examining the word contrast during the no-pressure trials, there were no significant group differences between control women and women with PVD, a finding that is incongruent with previous research. For example, participants with low back pain demonstrated increased activation of areas of the pain matrix as compared with control participants during a pain visualization task (Shimo et al., 2011). Eck and colleagues (2011) also demonstrated enhanced activation in pain structures for pain words read by migraine patients as compared with control participants. In an earlier study, migraine patients primed with pain words showed increased amplitudes in laser-evoked potentials for affective pain word primes as compared with somatosensory pain word primes, a finding that was not evident in the control group (Weiss et al., 2003). Perhaps, as suggested by the study conducted by Weiss and colleagues (2003), one reason for a lack of group differences in the current study was the use of somatosensory descriptors as opposed to affective ones. While this is certainly a possibility, it must also be noted that the findings by Weiss and colleagues (2003) are not unequivocal. A study comparing patients with a “functional pain syndrome” (fibromyalgia) to a chronic pain of known origin (chronic musculoskeletal pain) found that those with chronic musculoskeletal pain had increases in brain activity for affective as compared with sensory pain words; however there were no differences in brain activity between these word types in the
fibromyalgia group (Sitges et al., 2007). Another possible reason for the lack of group differences and the inconsistency with the literature is that the cited studies use words or visual stimuli in the absence of actual pain. The current paradigm applied an unpredictable and possibly painful stimuli immediately following each word, so both the PVD group and the control group were anticipating a potential pain stimulus. The words in the other studies may have been more apt to activate pain schemas, whereas those in the current study may have been related more to the experimental pain, thus causing activation in both groups.

### 6.3.5. Interaction of Word by Pressure

When collapsed across group, there were no significant two-way interactions between word and pressure at the whole brain level; however, with a SVC of the pain matrix, there were interactions present in the left MCC and the left postcentral gyrus (S1 area). Examination of the interaction effects revealed that, for both the MCC and postcentral gyrus, pain words were more activated than neutral words for the no pressure condition, but for the painful pressure condition, neutral words resulted in greater activation than painful words. The results of the no pressure condition were expected, as pain words demonstrated greater activation than neutral words in previous studies and in the current study in various areas when a directed search of word differences in the no pressure condition was conducted. Perhaps the higher activations found with neutral words during the painful pressure stimulus in the current study is due to stimulus saliency. This hypothesis supposes that there might be an increase in stimulus saliency as a result of the discrepancy between seeing a neutral word and receiving a painful stimulus. Saliency of the stimulus is significantly associated with activation in areas of the pain matrix. There was no significant difference between the words for the touch condition.

With respect to pressure in this interaction, results were as expected in the primary somatosensory cortex: the peak point of activation revealed higher overall levels of activation for pain and touch, as compared with no pressure. In the MCC, an area associated with affective and cognitive processing, the
touch condition resulted in significantly lower activation than the no pressure condition and there were no differences between the pain condition and the no-pressure condition. This unexpected finding might reflect increased activations associated with higher stimulus saliency in the pain and no-pressure conditions as compared with the touch condition. In the no-pressure condition, painful words may be particularly salient when no stimulation is applied. In the pain condition, there is high saliency associated with the application of a pain stimulus. Decreased activation during touch as compared with no pressure and with pain might be consistent with counter-irritation paradigms in which touching a painful area can reduce the pain sensation (Le Bars, 2002); perhaps touch can reduce the pain activations triggered by painful words. This hypothesis remains to be further explored.

6.3.6. Main Effect of Pressure

As predicted, there was a main effect of pressure. It was hypothesized that, for all participants, moderately painful stimulation (rated as a 4/10) would result in greater levels of activation than touch, which would result in greater levels of activation than no pressure. Consistent with this hypothesis, simple effects revealed the highest levels of activation for pain, followed by touch, and then by no pressure. Results from the present study, with respect to the main effect of pressure, were consistent with other studies examining experimental pain (e.g., Apkarian et al., 2005; Gracely et al., 2004).

Consistent with the literature on neural responses to pain, the main effect of pressure revealed significant activations throughout the pain matrix (ACC, S1, S2, insula, and areas of the PFC). In addition, there was activation outside of the classic pain matrix, in the occipital gyrus. In the S1 and S2 areas, activations were strongest for pain, followed by touch, followed by no pressure. The same effect was found in the ACC. There was no significant activation in the thalamus, which was unexpected; however, a meta-analysis revealed that 20% of studies on healthy individuals and 41% of studies on clinical pain conditions have not found activation in this region (Apkarian et al., 2005). There was also no significant main effect in the insula (although in the group level t-tests contrasting pain with touch and
baseline there was robust activation during the pain versus touch contrast and the pain versus no pressure contrast). Activation of the insula is found in 94% of studies on healthy individuals, but only 58% of studies on clinical pain conditions (Apkarian et al., 2005). Areas of the PFC showed activations and deactivations for all three pressure conditions. For example, all three conditions had activation in the right middle frontal gyrus, an area associated with attention. All three conditions showed deactivations in the left middle orbital gyrus, an area that has demonstrated deactivations irrespective of pain intensity and perception in a previous study (Oertel et al., 2012).

The largest cluster of activation in the main effect of pressure contrast extended from the left supramarginal gyrus to the left rolandic operculum, including areas OP1 and OP3. Findings of activation in the supramarginal gyrus are consistent with a number of other pain studies (e.g., Baciu et al., 1999, Ferraro et al., 2012, Friebel et al., 2011, Moulton et al., 2011); however, activations in this region are more likely to be found when pain is mechanical, as opposed to thermal (Lanz et al., 2011), as was the case in the current study. Another activation cluster contained peaks in the left superior medial gyrus, left SMA (BA 6), and left ACC, with highest activations in these regions associated with the painful stimulation condition. This same cluster of activation peaks was found in another study during the presentation of painful words (Eck et al., 2012). Consistent with the present study, activations in the precentral gyrus and SMA were found in the pain stimulation condition in both fibromyalgia patients and control participants (Gracely et al., 2002). Given that the pain stimuli were applied to the vulva, activation in the precentral gyrus is consistent with findings of an anal and vaginal motor region located on the dorsal surface of the precentral gyrus (primary motor cortex) in non-human primates (Grünbaum & Sherrington, 1901, in DiNoto et al., 2012). Areas of the motor cortex would also be expected to be activated as a means of preparing to withdraw from the pain stimulus (Shimo, 2011).

Activations were also present in the middle frontal and orbital gyri, making up the orbitofrontal cortex (OFC), which is proposed to be involved in tasks such as sensory integration, expectation, decision-making, and affective states (Kringelbach, 2005). Most of the activations in the frontal regions
of the brain the current study were lateralized to the right side of the brain. Lateralization to the right in
the frontal areas of the brain is consistent with previous findings that pain stimuli result in right
hemisphere lateralization in the middle frontal gyrus (Symonds et al., 2006). This right lateralization in
the frontal gyri is consistent with the hypothesis that there is perhaps a right lateralized attention system to
alert an individual to stimuli such as pain (Symonds et al., 2006). Increased activation in the middle
frontal gyrus during anticipation of pain has been found in other studies (e.g., Ochsner et al., 2006; Porro
et al., 2002; Porro et al., 2003; Zambreanu et al., 2005). The middle frontal gyrus may therefore be an
area where psychosocial variables might contribute to augmenting or diminishing the pain experience
through facilitating or inhibiting responding to pain. As painful stimuli were being unexpectedly applied
throughout the current experiment, it can be assumed that some of the brain activation may represent the
anticipation phase of the pain, particularly given the close temporal relationship between the word and the
pressure stimulus. The current study procedure, however, was not designed to be sensitive to the temporal
differences of the word and pressure stimuli, which would have been better captured by an alternative
methodology or other imaging methods such as MEG. Gu and Han (2007) showed that increased
activation in the medial frontal gyrus was associated with the process of rating pain intensity, even in the
absence of a painful stimulus. Studies have demonstrated a negative correlation between experimental
pain ratings and OFC neural activity (Derbyshire et al., 1997). Increased neural activations in the OFC
are associated with decreased pain ratings (Bantick et al., 2002; Valet et al., 2004) and with decreased
neural activation in regions of the pain matrix, including the thalamus, insula, and dorsal ACC
(Lieberman et al., 2004; Petrovic, Petersson, Hansson, & Ingvar, 2002; Wager et al., 2004), all of which
are areas that are connected with the OFC. Current findings of greater magnitude of deactivation in this
area for painful pressure are consistent with these previous reports in the literature (e.g., Banatik et al.,
2002; Derbyshire et al., 1997). It is postulated that increases in the OFC inhibit activations in these areas
of the brain, leading to decreased perception of pain (Bantick et al., 2002). Electrical stimulation of the
lateral OFC results in decreased pain related behaviours in rats (Zhang et al., 1997). Increased activation
in the OFC occurs when participants are distracted from pain, suggesting the role of this region in pain modulation (Apkarian et al., 2005). In reviewing the findings on pain and OFC activation, Hooker & Knight (2006) suggest that this area can inhibit pain sensation by increasing neural activity anticipation of a painful stimulus. Activation in the middle occipital gyrus and precentral gyrus has also been associated with early uncertainty in expectation of pain stimulus (Brown, Seymour, Boyle, El-Deredy, & Jones, 2007), which is consistent with the paradigm of the current study during which the priming word did not predict the subsequent stimulus. Activation in BA18, an area in the occipital lobe with significant findings in the present study, has also been associated with pain-related activation, but in the absence of a painful stimulus. This area was activated in low back pain patients in relation to their self reported pain during a task in which they were shown an image of simulated low back pain (Shimo et al., 2011). The middle occipital lobe has also been associated with rating pain intensity in the absence of a painful stimulus (Gu & Han, 2007).

Areas of the DMN also showed a main effect of pressure, including the angular gyrus, middle temporal gyrus, and precuneus, the latter of which is hypothesized to integrate somatosensory sensations and regulate motor coordination. Changes in these areas during the application of both painful and non-painful stimuli have been reported in the literature (e.g., Oertel et al., 2012). Consistent with the current study, deactivations in the middle temporal gyrus and precentral gyrus were noted during low pain stimuli (both pain and touch conditions in the current study), as compared to rest in healthy individuals (Kong et al., 2010). Deactivations have also been found in the precuneus in relation to anticipation of pain and in proportion to pain perception (Koyama et al., 2005). Consistent with a lack of significant group by pressure interactions in the current study, activation levels in the precuneus did not differ between healthy control participants and a group of patients with “severe” chronic pain (Malinen et al., 2010). In contrast with results of the current study, a study administering pain-related words during a distraction task found deactivations in the angular gyrus, mid-temporal gyrus, precuneus, and posterior cingulate cortex in healthy control participants (a normal finding for areas of the DMN), but not for migraine patients (Eck et
al., 2011). Other studies have also found activations in the DMN in pain patient groups, which is consistent with the hypothesis of increased baseline activity in the DMN in chronic pain (Lanz et al., 2011). Significant activation of the angular gyrus was reported during visceral pain stimulation in healthy participants (Baciu et al., 1999). In studies where participants looked at pictures of individuals in pain, the angular gyrus and left middle temporal gyrus were more significantly activated in the low back pain group compared to a healthy control group (Shimo et al., 2011).

6.3.6.1. Exploration of Activations & Deactivations Associated with Pressure

One of the strengths of the current study was the inclusion of a contrast between pain and touch, allowing for an examination of areas of the brain that are activated by pain without the confounding factor of touch. Many studies only examine pain in relation to a baseline, rather than to a touch condition. Contrasts comparing pain with a no-pain baseline during experimental pain reveals widespread activation throughout the ‘pain matrix;’ however, when pain is compared to a no-pain baseline, there are many other confounds that could be accounting for the activations. Comparing a pain condition to a touch condition provides more confidence that the activated regions are due to pain, and not just to a stimulus application. Pain resulted in greater activation than touch in many, but not all, areas of the pain matrix. This pattern is consistent with findings that the pain matrix can also be activated by non-painful stimuli (e.g., Lui et al., 2008; Mouraux & Iannetti, 2009). This contrast revealed higher activations for pain in the left MCC and left ACC, bilaterally in the insula, and bilaterally in the cerebellum. Activation in the cerebellum was located in regions associated with noxious stimulation (Lobule VI; Moulton et al., 2010). The cerebellum is hypothesized integrate affective processing, pain modulation, and somatosensory processing (Moulton et al., 2010). In addition, there was significant activation in the left supplementary motor area (SMA/Area 6), the brainstem (as reported in other pain studies, e.g., Afridi et al., 2005), the right precuneus, the occipital gyrus, and the right supramarginal gyrus. As described above, the increased activation in the occipital areas and precuneus during painful stimuli may be consistent with another study, which found
that areas of the occipital lobe are activated when looking at pictures of people in pain (Shimo et al., 2011). Robust activations in the forebrain and brainstem were evident during the contrast comparing pain with no pressure. This finding is consistent with a summary of findings in the literature that suggests that chronic pain patients have altered brain activations and circuitry in both the forebrain and brainstem (Schweinhardt & Bushnell, 2010). As with the main effect analyses, the thalamus was not activated in the contrast comparing pain with touch. The contrast for comparing touch with pain did not reveal any significant activations (which would represent a deactivation during the painful stimulus); however, activations during the contrast comparing pain to no pressure (i.e., areas of deactivation for pain) were evident in the angular gyrus, the middle temporal gyrus, the rectal gyrus, the middle orbital gyrus, the precuneus, and the occipital gyrus.

Consistent with previous studies examining non-painful pressure stimuli, areas that were activated for touch stimuli included many areas thought to make up the pain matrix, including the left and right MCC, secondary somatosensory cortex, thalamus, cerebellum, putamen, and SMA.

6.3.7. Study #1 Conclusions

Findings from this study support many of the findings in the neuroimaging pain literature. Pain results in widespread activation of areas of the pain matrix; however, when using touch as opposed to a no pressure baseline, pain activations were confined to a smaller number of regions, including the cingulate cortex, insula, thalamus, cerebellum, and the SMA. There were no longer significant activations in the somatosensory cortices or PFC, suggesting that these areas are not uniquely associated with pain. While controlling for pain perception by matching the groups on pain ratings, activations were similar between healthy control women and women with PVD. In whole brain analyses, control women had higher activations in the precentral gyrus, which perhaps reflects the increased pressures required to obtain a rating of 4/10. Directed searches at peak points revealed a smaller difference in activation between touch and pain at the S2, a finding that is perhaps consistent with allodynia in the PVD group.
Painful words and painful pressure both activated regions of the pain matrix, though the combination of painful words and pressure stimuli did not result in greater activation than neutral words with pressure stimuli, except in the left MCC and left post-central gyrus, where the mis-match in pain between word and pressure resulted in higher activations, perhaps reflecting the higher saliency of the stimuli when they are not matched (e.g., a neutral word with a painful pressure stimulus). The lack of significant findings in more widespread regions during pain word conditions may be due to the large magnitude of activation already present from the pressure, which is not significantly augmented by the addition of a painful prime. There were also no group differences in neural activation for painful words, which is inconsistent with previous literature (Shimo et al., 2011). The lack of significant group differences may be due to the nature of PVD pain, as it is intermittent and provoked, rather than continuous and spontaneous as many of the other conditions categorized as chronic.

6.4. **Study #2**

As described above, the second aim of the study was to compare women with PVD and control women on psychosocial variables (e.g., anxiety and catastrophizing), as well as to test whether anxiety and catastrophizing are correlated with neural activations during painful stimulation, and if so, whether there were group differences in the areas of the brain that are correlated with psychosocial variables.

6.4.1. **Anxiety**

Various types of anxiety were measured, including state and trait anxiety, anxiety sensitivity, and fear of pain/hypervigilance for both vulvar and non-vulvar pain reports. Women with PVD reported significantly higher trait anxiety than control women. Other studies have also demonstrated significant differences in trait anxiety (Payne et al., 2005), suggesting that women with PVD are more anxious than control women, even with respect to non-health related anxiety.

There were moderate effect sizes for state anxiety during the interview session, but not the fMRI testing session, likely because the fMRI testing session is a more stressful situation for all of the groups. It
may also be that state anxiety is elevated in women with PVD when they are talking about (as during the interview) or experiencing vulvar pain, but not when their attention is focused away from their vulvar pain. There are ample reports in the literature that women with PVD display higher levels of both state and trait anxiety as compared with control women (e.g., Nunns & Mandal, 1997; Nylanderlundqvis & Bergdahl, 2003; Payne et al., 2005).

There were no group differences in anxiety sensitivity, as measured by the ASI. Although anxiety sensitivity has been strongly associated with pain (Norton & Asmundson, 2004), other studies have also reported a lack of group differences between pain populations (including PVD) and control groups on this variable (Keogh et al., 2001; Payne et al., 2005), suggesting that anxiety sensitivity may not increase the likelihood of progression in all chronic pain conditions. Perhaps an anxiety sensitivity measure that specifically assesses gynecological symptoms might tap into group differences. PVD women in this study may have scored more similarly to controls on state-anxiety and anxiety sensitivity based on characteristics of the sample that was recruited. Those who participated in this study willingly consented to and volunteered for an fMRI study, an experimental protocol that requires people to be comfortable in a situation that is anxiety-provoking for many individuals. The experimental protocol was much more invasive (e.g., fMRI scan, vulvar testing) than many studies examining women with PVD. Given the experimental procedure, both groups may have scored similarly on state anxiety prior to the fMRI task, regardless of group membership. Also, participants were excluded if they experienced claustrophobia or panic disorder. Given the high comorbidity among anxiety disorders (Brown & Barlow, 1992), this exclusion criterion may reduce the likelihood of group differences on general, as opposed to pain-specific anxiety measures. In addition, there is much overlap between chronic pain and anxiety (Asmundson & Katz, 2009), and many other chronic pain studies do not exclude individuals with anxiety disorders. The sample collected may be under-representative in terms of level of state-anxiety or anxiety sensitivity in the general population of PVD-sufferers.
Based on the knowledge that preoccupation with pain is distinct from general preoccupation with somatic complaints and anxiety (McCracken, 1997), pain-specific anxiety measures were also completed by both groups. Women with PVD filled these measures out twice, once for their vulvar pain, and once for their worst regularly experienced non-vulvar pain. When asked about vulvar pain on the PVAQ, women with PVD scored higher on pain-related hypervigilance than did control women regarding their worst regularly experienced pain, but this finding did not hold when women with PVD were asked to report on their worst regularly experienced non-vulvar pain, although the effect size was in the moderate range. These findings are consistent with a previous study examining PVAQ scores in women with PVD (Payne et al., 2005). Consistent with increased anxiety in situations in which there might be anticipation of vulvar pain, women with PVD also demonstrated decreased confidence and self-efficacy regarding sexual intercourse when their partner initiates sexual activity. Also consistent findings in the PVD literature, pain-specific anxiety as measured by the PASS did not show significant group differences between PVD and control women for comparisons of vulvar or non-vulvar pain (e.g., Payne et al., 2005). Although scores on the PVAQ and PASS are correlated, both in the literature (e.g., McCracken, 1997; Roelofs et al., 2003) and in the present study ($r = .62 - .77$, $p’s < .001$), the PASS was not predictive of group differences. These findings suggest that women with PVD are more hypervigilant about their vulvar pain (as measured by the PVAQ) when compared to control participants’ worst regularly experienced pain, but they do not appear to be more hypervigilant about pain in general, and they are not more fearful of their vulvar or non-vulvar pain than are control women, as measured by the PASS. When examining effect sizes, it appears that PVD women may experience more cognitive-based pain-specific anxiety on the PASS for vulvar and non-vulvar pains, which may also reflect their tendency to catastrophize about their pain (see below). The lack of significant group differences on the PASS and the non-vulvar PVAQ differs from the pattern of results demonstrated in the general chronic pain literature (Carleton, Abrams, Asmundson, Antony, McCabe, 2009), perhaps because PVD is a chronic intermittent pain condition, rather than a constant or spontaneous pain condition. Also, the scores on the PASS total
for the PVD group were much lower than scores in low back pain patients in one study (Hadjistavropoulos, Asmundson, & Kowalyk, 2004).

The STAI-T and vulvar-pain specific PVAQ were chosen as correlates for the BOLD activation during pain stimuli based on findings that both trait and pain-specific anxiety/hypervigilance are associated with the maintenance of chronic pain.

6.4.1.1. Trait Anxiety and Neural Imaging

When the STAI-T was correlated with neural activations during pain, both groups (PVD and control) showed a significant positive correlation in the right middle frontal gyrus (part of the DLPFC). Increased levels of trait anxiety were associated with increased neural activation in the middle frontal gyrus, an area associated with attention; however, the cluster size of this finding was extremely low (k = 6), and this result should be interpreted with caution. Correlations between pain stimuli and brain areas associated with attention are consistent with a hypothesis put forth by Arntz, Dreessen, and De Jong (1994), suggesting attention may be a primary mediator of the effects of anxiety on the pain. In addition, the lack of significant neural correlations with trait anxiety is consistent with a study on healthy individuals, in which authors examined correlations between pain and trait anxiety, as measured by the STAI-T (Oschner et al., 2006). Perhaps differences in trait anxiety, as opposed to pain-related anxiety, are not highly correlated with brain activation during experimental pain. Correlations between STAI-T scores and pain-related measures of anxiety were not high (Appendix R), suggesting that the role of trait anxiety in pain processing may not be substantial. Despite this hypothesis, the present findings still suggest that it does play a small role in pain processing. Another study found that pain as a result of a noxious stimulus may be determined by the coupling of insular and brainstem activity immediately prior to the stimulus, and the coupling of these regions was found to be dependent upon trait anxiety (Ploner, Lee, Wiech, Bingel, & Tracey 2010).
The entire sample (N = 28) was also split into moderate/high versus low trait anxiety. The moderate/high anxiety group had significantly higher activations in the bilateral ACC. There were no activations that were significantly higher in the low anxiety group. This finding confirms that, regardless of whether individuals experience chronic pain, moderate-high levels of anxiety are associated with activation in the ACC, an area that has been linked to both emotional and cognitive processing to pain, in numerous studies (e.g., Apkarian et al. 2005; Rainville et al., 1997) as well as to heightened levels of anxiety (Bishop, Duncan, Brett, & Lawrence, 2004). Activation was also expected in the insula, as it has been suggested that it signals pain in anxious individuals (Paulus & Stein, 2006); however, no significant group difference was found. Increased trait anxiety has also been correlated with increased activity in the amygdala during pain expectation (Ziv, 2010). The lack of differences in these areas in the present study may have been due to the fact that the sample in the current study was not overly anxious.

6.4.1.2. Pain-Related Anxiety and Neural Imaging

When the vulvar pain specific PVAQ was correlated with neural activation during painful stimulation, women with PVD showed significant positive correlations in the right middle frontal gyrus (part of the DLPFC), right superior frontal gyrus, and left superior orbital gyrus, areas associated with attention and pain modulation. There were no significant activations in the ACC, which contrasts with research on women with irritable bowel syndrome (IBS). In IBS patients anxiety scores were associated with pain-induced activation in the anterior mid cingulate cortex and the perigenual ACC (Elsenbruch et al, 2010).

A positive correlation between pain hypervigilance and the right middle frontal gyrus (DLPFC) is consistent with results from a study examining anxiety using the Fear of Pain Questionnaire (FPQ) in healthy control participants (Ochsner et al., 2006). In the current study, however, the correlation was significant for women with PVD, but only marginally significant for the control group (p = .08). Right DLPFC activity has been associated with a weakened relationship to pain intensity and affect in the
insula, suggesting that the right DLPFC exerts active control of pain perception by modulating pain pathways in cortical and subcortical brain regions (Lorenz et al., 2003). Findings from the current study suggest that, when women with PVD and control women report the same pain intensity levels, women with PVD may be engaging greater attentional strategies to reduce the pain than are control women, which could be associated with increased activation in brain regions associated with cognitive/attentional control. Consistent with the current findings, the processing-efficiency hypothesis (Eysenck, Derakshan, Santos, & Calvo, 2007) suggests that, in order to maintain equivalent performance to those with low anxiety, high anxiety individuals may require greater activation of the DLPFC.

Activation of the superior frontal gyrus is consistent with a study examining anticipatory anxiety for a pain stimulus (Kalish et al., 2005). Uncertainty in pain paradigms is also associated with increased neural activation in the superior frontal gyrus (Brown et al., 2007). The superior frontal gyrus has also been reported as being associated with self-awareness. The positive correlation in this region for the PVD, but not control, group suggests that women with PVD may be experiencing higher levels of anxiety related to the pain stimulus. Emotional modulation of default network regions, including the superior frontal gyrus may prevent the decreased activation needed in these areas for optimal cognitive efficiency (Fales et al., 2008).

A positive relationship between anxiety and activation in the orbitofrontal region is also consistent with other studies examining pain and pain-related anxiety; the OFC has been hypothesized to play a role in regulation of responses to painful stimuli in fearful individuals (Lorenz et al., 2002; Ochsner et al., 2006).

There is also evidence in the literature that pain modulation by anxiety is associated with activation in the hippocampal formation, which increases the saliency of aversive events to prime the individual for adaptive behavioural responding (Ploghaus et al., 2001). Although the hippocampal formation was not activated in the anxiety correlation brain maps for control women or women with PVD, when high and low anxiety scores on the PVAQ were contrasted, there was a small activation (k =
6) in the right parahippocampal gyrus. This result is consistent with findings that persistent pain induces stress-damaging effects in the hippocampus (Duric & McCarson, 2006).

Both the women with PVD and the control women had significant negative correlations in the left superior frontal gyrus and the right angular gyrus (part of the DMN). The negative correlations in regions of the PFC indicate that lower levels of anxiety (PVAQ) are associated with increased neural activity in these regions. A study on catastrophizing also found negative correlations in the superior frontal gyrus during moderate pain levels (Seminowicz & Davis, 2006). In a study on pain-related words during a distraction task, the left angular gyrus was deactivated in healthy control participants, but not in migraine patients (Eck et al., 2011). This finding also holds for application of pain stimuli (Oertel et al., 2012). A study in which participants looked at pictures of individuals in pain found that the angular gyrus was more significantly activated in the low back pain group compared to a healthy control group (Shimo et al., 2011). Activation of this region was also reported during visceral pain in healthy participants (Baciu et al., 1999). The angular gyrus has also been associated with empathy (Vollm et al., 2006).

The findings of both negative and positive correlations within the pre-frontal cortex are reflective of the heterogeneity of this large region, and have been reported in other pain studies (e.g. Kong et al., 2010). Anxiety has been associated with both increased (Elsenbruch et al., 2010) and decreased (Bishop, 2007; Bishop, Duncan, Brett, & Lawrence, 2004) activation in attentional regions of the brain. The difference in the direction of correlations in the right and left superior frontal gyri may reflect some of the lateralization effects found in pain processing. Right lateralized processing of areas in the frontal gyrus during acute pain have been demonstrated, and this finding is consistent with the hypothesis that there may be an important attentional system that is lateralized to the right side of the brain that functions to alert individuals to infrequent, but relevant stimuli (Symonds et al., 2006). Others have also found that right and left DLPFC activity correlates with activations in different areas of the brain, with right DLPFC weakening the relationship between the insula and pain intensity, and left DLPFC activity reducing
connectivity in the medial-thalamic pathway (Lorenz et al., 2003). These findings suggest that the DLPFC modulates pain pathways in the brain (Lorenz et al., 2003).

6.4.2. Catastrophizing

Also consistent with previous findings, women with PVD catastrophize more about their vulvar pain and non-vulvar pain than control women, and 64% of women with PVD in the current study scored above the PCS cut-off score for chronic pain. There was no significant group difference on the magnification subscale of the PCS; however, this result is consistent with findings in the literature suggesting that specific components of catastrophizing may vary as a function of duration of illness (Sullivan, Sullivan & Adams, 2002). Magnification was the best predictor of pain and disability in a sample that was approximately 1 year post-injury (Sullivan, Stanish, Sullivan, & Tripp, 2002), whereas rumination was the best predictor at three years post-injury (Sullivan, Stanish, Waite, Sullivan, & Tripp, 1998), and helplessness in later stages (Vienneau et al., 1999). The average pain duration in the present study was 4 years, and both rumination and helplessness were significantly higher for women with PVD than control women. Women with PVD also reported catastrophizing more often about their vulvar pain than control women did about their worst pain.

Women with PVD reported higher levels of catastrophizing with respect to both their vulvar and non-vulvar pains as compared with control women on the PCS. These findings are consistent with other studies examining catastrophizing in women with PVD. Catastrophizing was measured prior to participant exposure to the painful stimuli, rather than during the fMRI portion of the experiment; however, research has demonstrated that catastrophizing assessed during a pain-free state is able to predict pain ratings to aversive stimuli up to six months later (Keefe et al., 1989; Sullivan, Bishop, & Pivik, 1995). In the absence of treatment, catastrophizing appears to remain stable across healthy and chronic pain populations (Sullivan et al., 2001; Sullivan, 2012). Contrary to these findings, other research suggests that catastrophizing scores that are measured in a trait-like manner may not actually be
predictive of pain ratings during an experimental procedure, but rather that catastrophizing measured in-vivo are more predictive of experimental pain (e.g., Burgmer et al., 2011; Edwards, Campbell, & Fillingim, 2005). Another research group found that catastrophizing scores obtained during heat, cold, and pressure pain testing were more predictive than trait catastrophizing scores for healthy controls and arthritis patients, but not for patients with temporomandibular pain (Campbell et al., 2010). In contrast to the above stated findings and to the current study, some studies have found no relationship between state measures of catastrophizing and experimental pain (Hirsh, George, Bialosky, & Robinson, 2008).

### 6.4.2.1. Catastrophizing and Neural Imaging

Findings indicate that pain-evoked brain activity is related to pain catastrophizing in healthy individuals and in women with PVD. While there was some overlap between groups in areas of activation, there were also significant differences between the groups. During pain stimuli of varying pressures, all resulting in a pain rating of 4/10, regions of the brain typically associated with affective and cognitive/attention areas of pain were correlated with catastrophizing (see below), a finding that was expected, as researchers have demonstrated that attentional strategies moderate the relationship between pain catastrophizing and exaggerated muscle tension in the area of pain (Quartana et al., 2007). Other work has suggested that greater catastrophizing is associated with increased attentional demands to the pain stimulus, specifically to allocating attention to processing negative aspects of pain (e.g., Crombez et al., 2004; Eccleston & Crombez, 1999; Valet et al., 2004) and more difficulty disengaging from pain-related cues (Van Damme, Crombez, & Eccleston, 2002; 2004). Increased catastrophizing is also associated with less effective functioning of the endogenous opioid system and top-down control of pain inhibition (Weissman-Fogel et al., 2008). Consistent with these results, the current study found increased activation in the PFC. Most areas associated with top-down control of pain (e.g., areas of the PFC) were negatively associated with catastrophizing for control women, with the exception two peak points in the right middle and inferior frontal gyri. This finding was reversed for the PVD group, where the majority of
the activations in the PFC were positively correlated with catastrophizing, with the exception of the right superior frontal gyrus.

To the best of the author’s knowledge, there has been one structural imaging study on catastrophizing and PVD, and three functional imaging studies on catastrophizing and pain, two examining individuals with fibromyalgia and one examining healthy control participants. Catastrophizing was positively correlated with neural activity in the hippocampal and basal ganglia regions in women with PVD (Schweinhardt et al., 2008). In healthy participants, pain catastrophizing during moderate pain (independent of neuroticism) was negatively correlated with activity in the DLPFC and medial PFC; in contrast, during mild pain, pain catastrophizing was associated with increased activity in the PFC, IC, and caudal ACC, which reveals neural correlates for the long known exaggerated affective processing of pain that results from catastrophizing with mild levels of pain. The authors concluded that the correlations with the more intense pain may reflect a failure to activate inhibitory controls during pain (Seminowicz & Davis, 2006). In patients with fibromyalgia, Gracely and colleagues (2004) found positive correlations between level of catastrophizing and the magnitude of neural activation for mild pain stimuli in brain structures that have been associated with pain processing, particularly the emotional and attentional aspects of pain. Catastrophizing in fibromyalgia patients during mild pain was associated with increased activation in S2, the cerebellum, the medial frontal gyrus, the mid-frontal gyrus, the pre-motor cortex, and the ACC. When the fibromyalgia participants were dichotomized into high versus low catastrophizers, the high catastrophizing group had significantly higher activations in S2, the ACC, the superior frontal gyrus, and the medial frontal gyrus. The contralateral inferior parietal lobe (IPL) was more activated in the high catastrophizing group; however the ipsilateral IPL was more activated in the low catastrophizing group.

For women with PVD activity in the DLPFC, an area associated with attention and modulation of pain, was positively associated with catastrophizing, such that higher catastrophizing corresponded with increased brain activation, a finding consistent with a study examining catastrophizing in individuals with fibromyalgia (Gracely et al., 2004). For control women, most peaks in the DLPFC were positively
correlated with catastrophizing, with the exception of one peak of activation in the right hemisphere, which was negatively correlated with catastrophizing. These findings are consistent with healthy control participants, which demonstrated positive correlations between catastrophizing and activity in the DLPFC during mild pain ratings, but negative correlations during moderate pain ratings (Seminowicz & Davis, 2006). It is possible the current study showed both positive and negative correlations because a 4/10 rating is the lowest possible rating in the moderate range (which is from 4-6 out of 10), thus there may be some overlap between findings of mild and moderate pain.

Consistent with a study on healthy individuals and catastrophizing, there were no significant activations in areas commonly identified as belonging to the lateral pain system (e.g., S1, S2, thalamus); however, at a very small cluster level (k = 1), there were positive correlations with areas of the basal ganglia (bilateral putamen in both groups and right caudate in the control group), such that higher catastrophizing was associated with higher levels of brain activation in this region. The basal ganglia play a role in acute and chronic pain (Borsook et al., 2010). This structure is involved in integrating sensory, emotional, and cognitive information between thalamic and cortical regions, as well as sensory input from the brainstem (McHaffie, Stanford, Stein, Coizet, & Redgrave, 2005). Dysfunctional cortico-basal ganglia-thalamic loops may contribute to maintaining chronic pain (Borsook et al., 2010). Increased grey matter density in this region has been found in women with PVD (Schweinhardt et al., 2008), a finding that suggests that this area is often active, perhaps due to continual modulation of the chronic pain state. The putamen has been associated with increased BOLD activity in both acute and chronic pain; however, the caudate shows a reverse effect in BOLD signal for chronic pain (Borsook et al., 2010). Somewhat consistent with these findings, there was no significant correlation between catastrophizing and activation in the caudate for the PVD group. There was a positive correlation between these variables in the control group. Consistent with the catastrophizing literature, findings suggest that higher catastrophizing results in increased processing of painful stimuli.
When women were classified according to whether they were high or low on catastrophizing, a number of brain regions showed significantly higher activations for the high catastrophizing group as compared with the low catastrophizing group. This was not explained by potentially lower pressure pain thresholds in the high catastrophizing group, as there were no significant group differences in pressure pain threshold or pressure applied to generate a pain rating of 4/10, and thus no significant difference in amount of pressure applied during the experiment. Others have demonstrated that, while catastrophizing is related to pain ratings, it is not related to nociceptive reflex thresholds (France et al., 2002), suggesting that catastrophizing alters the pain experience thorough brain mechanisms as opposed to spinal cord mechanisms. There were no significantly higher neural activations in the low catastrophizing group. Women who scored high on catastrophizing had higher activations in the left superior frontal gyrus, right middle frontal gyrus, left superior temporal gyrus, bilateral putamen, and left cingulate gyrus. None of the regions had a large cluster size, so results should be interpreted with caution; however increased neural activation in the cingulate gyrus and areas related to sensory and motor aspects of pain (e.g., putamen) are consistent with findings from the study on catastrophizing in fibromyalgia patients conducted by Gracely and colleagues (2004).

The significantly higher activations for high catastrophizing with the left cingulate gyrus and the left IC, areas associated with cognitive and emotional processing of pain, suggest that catastrophizing may influence pain perception thorough influencing the cognitive and affective aspects of pain. Higher activations for the high catastrophizers in the superior frontal gyrus and the cingulate cortex are consistent with findings by Gracely and colleagues (2004) who examined high and low catastrophizing in patients with fibromyalgia. A study examining catastrophizing in healthy individuals concluded that activity in the insula might represent a pain vigilance signal in people who are pain catastrophizers, a finding that is in line with results from the present study in which higher catastrophizing across both groups resulted in an increased magnitude of activation in the insula. The higher activations for high catastrophizers in the superior and middle frontal gyri are associated with self-awareness and integration of sensory information.
(Goldberg, Harel, & Malach, 2006). These are both areas of the DLPFC, and they have been associated with pain in numerous studies.

The superior temporal gyrus has been implicated in emotional processing, and is activated in other chronic pain studies (e.g., Gracely et al., 2002), as well as language processing studies (Vitacco et al., 2002). The superior parietal gyrus is activated during pain (e.g., Cook et al., 2004; Raij, 2005) and during painful words with distraction (Eck et al., 2011; Richter et al., 2010). The putamen has been associated with sensory aspects of pain; individuals with lesions in this area experience less activation in S1 and S2 (Tomycz & Friedlander, 2011). In the present study, high catastrophizers had significantly greater activation in the putamen, suggesting that level of catastrophizing does impact some areas associated with the sensory component of pain. Contrary to previous chronic pain findings (Gracely et al., 2004), but consistent with a study on healthy control participants (Seminowicz & Davis, 2006), there were no significantly higher activations for the high catastrophizing group in S2. Gracely and colleagues (2004) reported an increased magnitude of activation in S2 for the high catastrophizing group during a mild pain stimulation contrast. This may account for some of the differences in findings between the current study and Gracely’s 2004 study, as the correlation between mild pain and catastrophizing results in activation of a greater extent of brain regions outside of the PFC than moderate pain.

6.4.3. Study #2 Conclusions

Findings of increased correlations in the PFC for the PVD group as compared with the control group are consistent with findings from a meta-analysis suggesting that pathways outside the spinothalamic tract may activate the PFC regions, and these other pathways (e.g., spinohypothalamic, spinoreticular) might become more important in chronic pain states (Apkarian et al., 2005). Increased correlations between neural activation during pain and anxiety and catastrophizing suggest that women with PVD have stronger cognitive, emotional, and introspective aspects to pain.
It has been suggested that catastrophizing needs to be examined in the context of other variables. A study examining the influence of fear of pain and catastrophizing on pain-related outcomes found that, when the variables were entered into a model together, fear of pain, but not catastrophizing accounts for pain ratings (George et al., 2006). The current study found that, when taking into account catastrophizing, anxiety was still associated with activations in the right and left middle frontal gyrus. When catastrophizing was examined taking into account anxiety, activations remained in the superior frontal gyrus and middle frontal gyrus. Although not a main purpose of this study, these analyses suggest that both anxiety and catastrophizing affect pain processing when entered into analyses together. The current author agrees with the need to further examine the psychosocial variables in relation to one another, particularly given their overlap of correlations in the frontal region, adding to the theory that both anxiety and catastrophizing measures are related to attention. These regions are associated with a variety of emotional and cognitive processes and activations remain significant for both pain-anxiety (PVAQ) and catastrophizing when controlling for the presence of the other variable. The measurement of anxiety and catastrophizing as differing constructs, despite high correlations, is consistent with findings in the literature that have demonstrated that catastrophizing is a unique and independent construct (Sullivan et al., 2001).

6.5. Study #3

Women with primary and secondary PVD did not differ significantly in age, parity, or hormonal contraceptive use. Although there were no differences in sexual functioning as measured by the FSFI (consistent with Sutton et al., 2009), women with primary PVD reported significantly less intercourse attempts per month, less confidence initiating and engaging in intercourse, and they initiated intercourse significantly less often than women with secondary PVD. There were no group differences in the percent of the time intercourse was painful, reported pain during intercourse or during the gynecological exam, or duration of the pain following intercourse; however, consistent with previous studies, women with
primary PVD were more sensitive to pain (e.g., had lower pressure pain thresholds) at the vulvar vestibule than women with secondary PVD (Sutton et al., 2009). Previous research has also demonstrated increased sensitivity to pain on a non-genital site (Granot et al., 2004b), and increased pain ratings at vulvar and non-vulvar sites in primary as compared with secondary PVD (Heddini, Bohm-Starke, Nilsson, & Johansson, 2012).

Consistent with previous research, women with primary PVD reported higher levels of trait anxiety, as measured by the STAI-T (Granot et al., 2004a). The current primary PVD group also reported higher state anxiety at the time of the interview. The primary group also reported increased anxiety sensitivity, total score and cognitive subscale as measured by the ASI, and increased levels of cognitive pain anxiety for both vulvar and non-vulvar pain, as measured by the PASS. They had higher overall levels of pain-anxiety for vulvar pain on the PASS. With respect to hypervigilance, as measured by the PVAQ, the primary group had higher levels of non-vulvar pain vigilance, but both groups scored similarly for vulvar pain vigilance. Taken together, these findings suggest that women with primary PVD have greater levels of general anxiety: trait, state, and anxiety sensitivity. They also tend to report higher levels of pain-specific anxiety for both vulvar and non-vulvar pain, although not higher levels of hypervigilance to vulvar pain than control women. Measures with subscales revealed that the differences tend to be driven by the cognitive domains of anxiety. Consistent with this finding is higher levels of catastrophizing as measured by the PCS. When examined using the PCS, women with primary PVD report more vulvar-specific and non-vulvar pain catastrophizing.

Women with primary PVD reported greater menstrual pain, consistent with a previous study (Granot et al., 2004a). Although the groups did not differ significantly in pain duration, there was a large variation in pain duration. As pain duration has been suggested as a possible confounding variable in comparisons between these two pain groups (Goetsch, 2007), it was included as a covariate in the imaging analyses to account for individual differences in duration. Women with primary and secondary PVD had brain activations in many similar areas, including bilateral activation of the putamen, insula,
thalamus, pallidum, and MCC. Both groups also had activation in the right inferior parietal lobule, right post-central gyrus, and the right rolandic operculum. Both groups had deactivations in the left rectal gyrus.

Activation in the insula, thalamus, and MCC were expected, as these areas are associated with emotional and cognitive processing of pain. Although the ACC is more commonly reported, the literature suggests that the cingulate cortex is a region that still remains to be thoroughly divided, and characterizing the structural heterogeneity of this region has been a major challenge (Vogt, 2009). Activation of the postcentral gyrus (S1 area) was also predicted, though this region does not consistently demonstrate activation in pain related studies (Apkarian et al., 2005), with the area more commonly activated in control groups (75% of studies) as compared to chronic pain patients (28% of studies). The S2 (rolandic operculum) also showed significant activations for both of the PVD groups; this region is only activated in 20% of studies examining clinical pain conditions (Apkarian et al., 2005). In a meta-analysis, Friebel and colleagues (2011) found activation in the rolandic operculum (S2 area) for both experimentally induced pain and chronic neuropathic pain; however, contrasts between the two revealed that the activations in this region were significantly higher for the neuropathic pain.

Activation in the inferior frontal lobe has been found in other chronic pain studies (Cook et al., 2004; Giesecke et al., 2004; Gracely et al., 2002), including a previous study on PVD (Pukall et al., 2005). The inferior parietal lobe is hypothesized to play a role in hypervigilance to nociception (Hsieh et al., 1995), which is consistent with the high levels of hypervigilance reported in both PVD groups. The lateralization to the right side in the inferior parietal lobule is consistent with findings from Symonds and colleagues (2006), demonstrating right lateralization of pain processing occurring in some areas of the brain, including the IPL.

The putamen, a structure located in the basal ganglia, has been associated with acute and chronic pain processing in numerous studies (reviewed in Borsook et al., 2010). A recent study examining pain activations in healthy control participants used structural connectivity to find connections between the
putamen and regions of the pain matrix involved in sensory-motor processing, as well as cognitive and affective regions (Starr et al., 2011). The putamen is involved in the integration of somatosensory and motor information for nociceptive stimuli (Bingel et al., 2004), and has been shown to be activated based on pain intensity, as opposed to stimulus intensity, and is not present with non-painful stimulation (Coghill et al., 1999; Downar et al., 2003; Oertel et al., 2011). A study on fibromyalgia patients showed increased grey matter volume in the putamen (Schmidt-Wilcke et al., 2007), and the authors suggest that this may be a result of continuous pain input producing increased activation and eventually increases in the structure. The pallidum, also part of the basal ganglia, is also involved in pain processing, with neurons that receive a large proportion of the signals generated by the unmyelinated primary afferent nociceptor pathway (Braz, Nassar, Wood, & Basbaum, 2005).

Women with secondary PVD had activations in the left postcentral gyrus, left rolandic operculum, and left SMA and deactivations in the left and right middle orbital gyrus; however when contrasts were run to test for significant group differences, these areas were not significantly greater for women with secondary PVD than for women with primary PVD. This finding highlights the importance of statistical testing for examining group differences, as activation maps are generated by a specific $t$-value cut-off, and groups do not have to be significantly different from one another for one group to just pass the $t$-threshold and the other to be just below it.

Activations in the left SMA are associated with motor responses, and the MCC and SMA are thought to connect in order to process and execute avoidance and escape reactions to pain (Vogt et al., 2003). The SMA is often activated during painful stimulation in healthy control participants and in some chronic pain patients (Friebel et al., 2011; Gracely et al., 2002); however, a meta-analysis of chronic neuropathic pain studies did not reveal activations in the SMA, suggesting that perhaps persistent stimulation results in a helplessness reaction in which pain cannot be avoided, and thus the avoidance activation stops functioning (Friebel et al., 2011).
Deactivations in the middle orbital gyrus (bilaterally) were evident in the secondary PVD group. There is considerable individual variability in the orbital-frontal region of the brain (Kringelbach & Rolls, 2004), leading researchers to suggest that the orbital frontal cortex be considered, both cytoarchitecturally and functionally, as the orbital and medial PFC (Ongur & Price, 2000). Deactivations in the OFC during painful stimulation are consistent with a study by Oertel and colleagues (2012), who found deactivations in this area irrespective of intensity and perception of the stimulus. Deactivations in the rectal gyrus are also consistent with findings by Oertel and colleagues (2012).

When the pain-none contrast was examined between groups, revealing areas of statistically significant differences, women with primary PVD had higher activations than women with secondary PVD in the left MCC, which is consistent with greater cognitive processing of pain stimuli for women with primary PVD. They also had greater activation in the right putamen, the left middle frontal gyrus and the left middle occipital gyrus.

Areas of activation are consistent with other studies examining pain processing, in that areas of the pain matrix were activated; however, a test examining statistical differences in response magnitude revealed greater emotional and cognitive pain processing in women with primary PVD. As might be expected from findings of greater psychosocial dysfunction and greater magnitude of neural activation in emotional and cognitive pain processing areas, women with primary PVD report less improvement and recovery in a variety of treatments than women with secondary PVD (Heddini et al., 2012). Unfortunately, the group did not report their findings by treatment type, thus it is not clear whether CBT treatments are more effective for the primary PVD group, as hypothesized would be the case by the findings of the current study. Increased central sensitivity for women with primary PVD may also explain the increased success rates of a localized treatment, vestibulectomy, for women with secondary PVD (Bohm-Starke & Rylander, 2008).

The current findings add to the literature that the two subtypes may develop from different etiological pathways (Goetsch, 1991; Granot et al., 2004a) and/or be maintained by different mechanisms.
Previous studies found that women with primary PVD may have developed PVD as a result of a congenital neuronal hyperplasia in urogenitally derived tissue (Burrows et al., 2008) or due to an MBL*B gene polymorphism combined with an environmental trigger such as friction with penetration (Babula et al., 2008).

6.5.1. Study #3 Conclusions

While this study is the first neural imaging study to examine women with primary and secondary PVD, more research is needed in order to fully understand the etiological processes, maintenance, and progression of these subtypes. This study helps to inform treatment options by highlighting the greater magnitude of emotional processing areas in women with PVD. Paired with findings of greater anxiety, both general and pain related, particularly cognitive aspects of anxiety, the findings suggest that perhaps women with primary PVD are best served by a CBT-type of intervention to address their negative cognitions and enhanced emotional processing of pain stimuli at subjective rating levels that are the same as secondary women with PVD. They might also benefit from treatment aimed at assisting with emotional regulation. Mindfulness-based therapies have also proven effective (e.g., Brotto, Basson, Carlson, & Zhu, 2012). Results of this study are consistent with the proposition that PVD be broken into subtypes based on temporal onset. Although there are many similarities between these proposed subtypes, an understanding of the differences that exist could assist in developing more successful treatments.

6.6. Limitations

The primary limitation, which is true of all fMRI research, is the problem of localization and labeling of anatomical regions (see for example, Brett et al., 2002). While some regions are more straightforward (e.g., the somatosensory cortex), others are far more complex and there is little agreement regarding the relationship between cytoarchitecture and anatomy (e.g., PFC). While the current study provided coordinates as a means of allowing readers to draw their own conclusions about the label associated with the area of activation, there are still problems with localization; because it is based on
normalization techniques and templates, it can be difficult to compare labels from different studies. Sulci in the brain tend to be highly variable between subjects, and the use of anatomical labels can be misleading. It is important to note that no conclusions can be made regarding cause-and-effect relationships between the variables, as the study was not longitudinal. Therefore, it cannot be concluded, from this study for example, that catastrophizing causes changes in neural processing in cognitive or affective regions of the brain. What is known in the literature, however, is that interventions such as CBT, which targets maladaptive thinking and negative emotions, demonstrate reversals in grey matter density, suggesting that cognitions and emotions play a role in maintaining pain (Jensen et al., 2012; Rodruigez-Raecke et al., 2009).

Other limitations associated with fMRI testing included items that may have increased movement or exhaustion during the testing session. For example, the use of verbal pain ratings during the fMRI testing session could have contributed to increased movement. Movement associated with making a verbal pain rating is not ideal for scanning; however, participants were trained in providing the ratings without moving their mouths excessively, and ratings were given many seconds after the end of the stimuli were presented. Head motion can produce changes in signal intensity, which is a serious confound in fMRI studies (Friston, Williams, Howard, Frackowiak, & Turner, 1996). To address this limitation, movement regressors were entered into the analysis, and data were examined for motion during a quality control check. The length of time in the scanner, which was required to conduct the three runs, was also a potential limitation, as participant movement and exhaustion are more likely with longer protocols.

Further, the nature of the testing required that there be constant contact of the labia in order to apply the pain stimulus, thus, the no pressure condition was reflective of no pressure at the vulvar vestibule, but a constant pressure was applied at a very close body site. This is a very important point to emphasize, as it may have reduced the robustness of the results by having a no pressure condition that did not actually reflect what it was purporting to measure, thus minimizing the differences in activation between “no pressure” and pain or touch stimuli. Important limitations in the experimental protocol also
included a lack of control for menstrual cycle phase at testing. This was due to the financial cost and booking restrictions involved in the imaging session; however, menstrual phase information was collected, which revealed no between group differences in phase of menstrual cycle during sensory testing.

Another major limitation comes from the pain literature in general, as well as for the current study, which is the difference between experimental pain and clinical pain. For example, clinical pain is less controllable than experimental pain. One of the strengths of the current study was the attempt for experimental pain to replicate clinical pain in the PVD group through application of the pain stimulus to the vulvar vestibule, using an instrument that has been validated to mimic pain during intercourse (Pukall et al., 2004). The study was also limited based on the participant pool. The majority of the sample was collected from an undergraduate population, resulting in a young and highly educated group of participants. A young sample may not generalize to older women with PVD, as there is ample evidence to support that pain is processed differently across the lifespan (e.g., Gagliese, 2009). There is also evidence to suggest that catastrophizing changes with age, such that it is more highly associated with emotional processing in young adults and with sensory processing of pain in older adults (Ruscheweyh, Nees, Marziniak, Evers, Flor, & Knecht, 2011); the current sample may not be a true representation of the correlations between neural activation during pain and catastrophizing. The sample was also collected to be as pure a sample as possible with respect to comorbid diagnoses (pain, mental, or physical health). While this practice was advantageous to ensure that the results are related to PVD and not some other problem, it also limits the generalizability of the results, as many women with PVD have comorbid diagnoses (e.g., Masheb et al., 2005; Ponte et al., 2009). Future research would benefit from collecting samples of PVD and control women who are matched on comorbidities rather than excluding participants for experiencing comorbid problems. One further limitation is the failure to ask detailed questions about birth control methods, including types of hormonal contraceptives and whether pain was exacerbated or improved with condom use (suggestive of either a latex or sperm sensitivity/allergy).
Finally, one of the major statistical limitations of the current study is the small sample size, which was fairly typical of an fMRI study, but limits the type of analysis that can be performed, as well as the sensitivity to detect significant differences. Sample size was chosen based on numbers typically found in the neuroimaging literature and based on considerations of cost and time; however, these numbers did not approach the sample size determined by power analyses for the psychosocial measures. Studies with a larger sample size would permit the necessary power to run more complex statistical analyses, perhaps leading to a model that examines the relationship between pain variables, neural correlates of pain, and psychosocial functioning in women with PVD. Power analyses suggest samples sizes of at least 64 participants per group to detect medium effect sizes and a significance level of \( p < .05 \) in a t-test (Cohen, 1992). Despite having a much smaller sample size, the current study was able to detect some robust effects, and the use of effect sizes (Cohen’s d) helped to offset this limitation and demonstrated moderate to high effect sizes on many variables. This finding suggests that future research in this area, using larger sample sizes, is warranted.

It is also important to note that activations in the pain matrix also overlap with areas of activation found in fMRI studies examining orgasm and arousal. For example, female arousal has been associated with areas involved in cognitive and emotional processing such as the ACC, OFC, medial PFC, inferior frontal lobe, IC, thalamus, and amygdala, as well as areas in the occipitotemporal cortices (Karama et al., 2002; Park, Kang, Seo, Kim, Ryu, & Jeong, 2001). Female orgasm and pleasurable clitoral self stimulation has also been associated with activations of regions similar to those activated during pain, with the exception of the PFC regions. Orgasm activates the amygdala, ACC, IC, basal ganglia, and hippocampus (Bianchi-Demicheli & Ortigue, 2007; Komisaruk et al., 2004). Such overlap in function is a reminder that brain regions do not activate as direct responses to a single stimulus, but rather activate to multiple types of input in a complex and interrelated fashion.
6.7. Implications and Future Directions

During the completion of this study, new and exciting neuroimaging techniques have emerged that warrant exploration with a PVD sample. The current study examined activations of brain areas in isolation of one another, connectivity analyses will provide further insight as to how the brain areas are connected and interact with one another, and whether these connections are dysregulated in PVD women. Spinal imaging to examine top-down descending pain mechanisms will also be extremely relevant for future imaging work on women with PVD, and may help to further explain the results of DNIC function in women with PVD (Johannesson et al., 2006; Sutton, Pukall, & Chamberlain, 2011).

Further understanding of the underlying neural mechanisms involved in the pain of PVD can help in discovering more about the etiology, maintaining factors, and appropriate treatments. With respect to etiology, prospective studies on women with risk factors (e.g., women carrying the MBL*B gene polymorphism) can examine whether there are structural and/or functional differences that precede the development of PVD.

Other variables involved in the pain process should be correlated with neural activation during pain (e.g., somatization, self-efficacy, partner response) in order to be examined as possible maintaining factors. New research and thoughts about the fear-avoidance model suggests that the next step in understanding chronic pain is to examine this model from a perspective that includes motivation and self-regulation (Crombez, Eccleston, Van Damme, Vlaeyen, & Karoly, 2012). Individuals who experience chronic pain tend to have disrupted goal attainment due to pain (Crombez et al., 2012); for example, women with PVD experienced reduced sexual and relationship functioning, thus pain may interfere with goals of intimacy or pleasure. This hypothesis is consistent with current findings of reduced self-efficacy for some sexual experiences in women with PVD, but further exploration is warranted, as goal attainment has not to date been specifically examined or discussed in women with PVD.

New literature on catastrophizing suggests a communal coping model, such that catastrophizing is viewed as an adaptive strategy in the short term to elicit the help of others, but that it is less adaptive in
the long run, resulting in less support (Sullivan, 2012). Partner variables should also be examined through neural imaging paradigms, such as exploring pain responses when viewing a picture of one’s partner or hearing the partner’s voice.

Findings from the first study are consistent with the literature and suggest that painful words activate pain related areas in the brain as compared with neutral ones. As mentioned by Richter and colleagues (2010), these findings suggest that pain-related words have the capacity to change central nervous processing. These changes may alter pain processing through associated learning. This finding has implications for clinicians, patients, and partners of patients, as the words they use may contribute to associations that activate pain areas in the brain. An interesting new line of research would be to examine the neural correlates of sexual words for women with PVD to see if these types of words also activate areas related to pain. It is hypothesized that sexual words may prime the pain matrix for women with PVD due to the learned association between sexual activity and pain. This line of research would be useful in determining whether sexual versus painful stimuli prime women with PVD for experiencing enhanced expectations and enhanced processing of pain during sexual encounters. Positive findings would further support the role of psychotherapy in the treatment of PVD.

With respect to treatment, disrupted brain function suggests the appropriateness of centrally-acting medications for pain; however, further work on neural circuitry and brain chemistry should be conducted. Also, the findings from this study provide further evidence that psychological processes are implicated in pain, evidence to support the usefulness of psychological interventions. Imaging studies examining brains before and after CBT are just beginning to emerge, and this study is consistent with the literature that psychological processes can serve to enhance pain. Studies of pre- and post-treatment imaging are in their infancy. It would be extremely useful to examine women with PVD before and after treatments such as CBT, mindfulness, and PFP to assess for differences in neural activation and structure of the brain post-treatment, and whether those changes correlate with any measured psychosocial or psychophysical changes.
Although all of the above stated directions should include subgrouping of primary and secondary PVD, with respect to further research specifically on women with primary and secondary PVD, the next appropriate step, and one that our research team is planning, is to conduct a structural imaging study examining whether there are differences between these groups in brain structure.
Chapter 7. Conclusions

The results of the above studies replicate numerous studies in the literature demonstrating that women with PVD experience hyperalgesia and allodynia at the vulvar vestibule, as well as decreased psychosocial functioning, including heightened pain-related anxiety and catastrophizing, and reduced sexual functioning. While a previous imaging study on women with PVD demonstrated increased neural activation to painful pressure as compared with control women, the present study found that, when subjective pain rating was held constant, as opposed to the applied pressure levels, there were only two significant group differences in neural activation of the pain matrix at the whole brain level, both of which revealed higher activations for control women. Findings from the current study used neural imaging to add support to the QST literature suggesting the presence of hyperalgesia in women with PVD. Overall, findings for the main effect of pressure were consistent with the pain literature; however, they added to the pain literature through comparison of pain to both baseline and touch conditions, a comparison that is not often conducted in pain studies. Findings suggest that the lateral pain system is not exclusive to pain stimuli. Also consistent with the literature, painful words activated areas of the pain matrix; however, they did not result in increased magnitudes of activation when paired with painful or touch stimuli, and there were no group differences in activation. The lack of group differences are inconsistent with the literature, but may reflect anticipation responses to pain due to the current paradigm pairing both the neutral and pain words with painful stimuli. Further research is warranted to examine the role of attention and priming in the PVD pain condition, and some exciting new lines of research have been suggested above.

When anxiety measures were examined in relation to moderately painful stimulation, there were few significant correlations between pain and trait anxiety for either group. There were more significant correlations in the frontal lobe region for women with PVD as compared with controls on a measure of pain hypervigilance. There were also significant correlations between catastrophizing and pain, particularly in frontal lobe; however, despite substantial group differences in catastrophizing on the PCS
there were few group differences in correlations between catastrophizing and neural activation. When groups were split into high versus low anxiety, there was a significant activation in the parahippocampus for high PVAQ scorers and in the ACC for those high on trait anxiety. High catastrophizers had increased activation in the middle frontal cortex. There were no significant correlations with the lateral pain system, a finding that is consistent with previous neuroimaging studies on catastrophizing and pain (Gracely et al., 2004; Seminowicz & Davis, 2006). Brain activations during pain that were correlated with psychosocial measures are consistent with their role in the cognitive and emotional processing of pain.

Exploration of women with primary and secondary PVD revealed significant differences in pain threshold, psychosocial functioning, and neural activation, with women with primary PVD faring worse than women with secondary PVD. This supports findings in the literature that suggest that these two subtypes of PVD may differ in etiology; however, studies examining brain function and structure prior to the development of the pain condition are necessary to further this hypothesis. This study does provide evidence that these two groups differ in maintaining factors, as women with primary PVD showing greater cognitive and emotional responses to pain using self-report and more objective (e.g., neural activations) data.

The results of the current studies provide support for findings of hyperalgesia and allodynia in women with PVD. They also support the role of anxiety and catastrophizing in augmenting the experience of pain in this condition. Finally, they help support the re-classification of PVD into subtypes based on temporal onset (primary versus secondary), by demonstrating differences in neural activations for these two groups. Future research should continue to explore neural activations associated with psychosocial functioning with the aim of determining potential therapeutic targets. Further exploration of the role of attention and primes that might enhance pain and negative coping in sexual situations will also be an important future direction for women with PVD. New imaging techniques can assist in further understanding temporal aspects of pain processing and how areas of the brain interact with each other and with psychosocial factors in the process of facilitating and inhibiting pain responses.
References


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185


doi:10.1126/science.277.5328.968


doi:10.1016/j.jpsychores.2008.02.018


doi:10.1097/AOG.0b013e318180965b


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Appendix A

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<thead>
<tr>
<th></th>
<th>Painful Word</th>
<th>Neutral Word</th>
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<tbody>
<tr>
<td>Painful Pressure</td>
<td>Condition 1 (pain_pain)</td>
<td>Condition 2 (pain_neutral)</td>
</tr>
<tr>
<td>Touch Pressure</td>
<td>Condition 3 (touch_pain)</td>
<td>Condition 4 (touch_neutral)</td>
</tr>
<tr>
<td>No Pressure</td>
<td>Condition 5 (none_pain)</td>
<td>Condition 6 (none_neutral)</td>
</tr>
</tbody>
</table>
Appendix B

Hypotheses Associated with the Factorial Design in Study #1

**Main Effect of Pressure.** It was hypothesized that pain would result in a higher magnitude of activation in the affective regions of the pain matrix than would touch, and touch would result in a higher magnitude of activation than in the no pressure condition. Simple effects were also examined in order to examine activations and deactivations specific to pain and touch. It was predicted that contrasts examining the effects of pain compared with those of touch will result in fewer significant activations than contrasts examining the effects of pain compared with no pressure.

**Interaction: Pressure x Group.** It was hypothesized that women with PVD would have higher neural activation in affective areas of the pain matrix (e.g., insula, ACC) than control women for pain, touch, and no pressure conditions, regardless of word presentation. Further, the difference in magnitude of activation between pain and touch was hypothesized to be smaller for the PVD group, as previous research has demonstrated that non-painful stimulation can result in increases within the pain matrix for chronic pain patients (allodynia).

**Main Effect of Word.** It was hypothesized that, for both groups painful words (i.e., the attention to pain condition) would result in higher neural activation than neutral words for pain, touch, and no pressure conditions.

**Interaction: Word x Group.** It was hypothesized that neural activation would be greater for women with PVD as compared with controls for all conditions containing painful words.

**Interaction: Pressure x Word.** It was hypothesized that painful words would elicit significantly greater activation than neutral words in the no pressure condition, but the difference between painful and neutral words would be of less magnitude in the pain and touch conditions.

**Interaction: Pressure x Word x Group.** It was hypothesized that for the PVD group painful pressure paired with painful words would result in the greatest magnitude of neural activation, followed by painful pressure and neutral words, which would not differ significantly from touch pressure and painful words. For the control group, it was hypothesized that painful pressure paired with painful words would result in the greatest magnitude of neural activation, followed by painful pressure and neutral words. Touch conditions were hypothesized to result in less neural activation than painful pressures for control women, regardless of whether they were paired with a painful or neutral word.
Appendix C

Opportunity to Participate in Exciting Psychology Research at Queen’s!

Who is eligible?
✓ All women over the age of 18, single or in a relationship
✓ Women’s partners

What studies are available?
✓ Couples study
✓ Blood flow imaging study for women
✓ FMRI study for women
✓ Treatment study for women with sexual pain
✓ And more!

All information is strictly confidential

**Compensation Provided**

Interested?
For more information, please contact the Sexual Health Research Lab

(613) 533-3276
SHRL@queensu.ca
Appendix D

Telephone screening interview: DNIC study  Participant ID # __________

Date of call: _____________________ Called participant: _____ Participant called: ______

RA initials: __________________________

1. How did you hear about this study?
   1) Newspaper ad: Which one? ____________________________________________
   2) Poster: Where? ______________________________________________________
   3) Word of mouth
   4) Doctor’s Office
   5) Other: How? ________________________________________________________

Study information
**Before beginning ASK THE WOMAN if her pain is genital (opening to vagina) or pelvic (near cervix or cramping) in nature. If it is ONLY pelvic explain that that is not the type of pain that we are studying. This will save you and her a lot of wasted time!**

I am just going to tell you a bit about why this research is being done and then explain in detail exactly what your participation entails. Please interrupt if you have questions.

The main goal of this study is to determine differences in pain characteristics in women with provoked vestibulodynia (PVD) and control women. PVD, formerly termed vulvar vestibulitis syndrome (VVS) is the most common form of genital pain, affecting about 12% of women in the general population. Despite the prevalence, we still do not know exactly what causes or maintains this pain. It is hoped that the results of this study will provide further information about the underlying causes and of PVD as well as things that might make the pain worse. We are hoping that this study leads to some new possibilities for treatment options.

Your participation in this study involves one appointment at the Kingston General Hospital for a gynecological examination and a separate appointment at the Sexual Health Research Laboratory in the Department of Psychology at Queen's University and the Queen’s MRI Facility. For the appointment at the hospital, you will be seen for about a half-hour by a female gynecologist and a female research assistant. The second part consists of an interview and some questionnaires, a sensory testing session, and an fMRI session. All together this should take approximately 3 hours to complete.

The interview will be done by a trained female researcher. The interview will cover information such as sociodemographics, medical history, vulvar pain history and pain characteristics (if you suffer from chronic genital pain), and sexual and relationship functioning. There will also be questionnaires on a computer asking about pain and sexual and relationship functioning. You are under no obligation to answer any questions that you feel uncomfortable answering.
The sensory and fMRI testing will be done by a trained female researcher who conducts the interview along with another research assistant present to run the computer and record ratings. FMRI facility staff will be present and may include both males and females. The sensory testing session consists of assessing pressure pain thresholds (e.g., when do you first feel pain) at the vulvar vestibule (the vaginal opening). The pressure increases in small increments and will stop increasing at any point if the pain becomes intolerable to you. We do not increase to a standard pressure for all the participants; it is entirely based on your own levels of pain tolerance.

For all sections of the sensory testing, the researcher will ask you at each time she applies a stimulus to your body if you feel pain or not and will ask you to rate the intensity and unpleasantness of the stimuli on scales. Although some pain will be experienced during this examination, no health risks are posed, and the painful sensations do not last for long periods of time. You are able to stop or control the session at any time. For your time and inconvenience, you will be reimbursed 100.00$ upon completion of all parts of the study.

**Do you have any questions?** Answer any questions the participant may have.

**Are you interested in seeing if you are eligible for participating in the study?**

**YES** → Thank them and ask for their full name: ______________________________

**NO** → Thank them for their time, and ask them to feel free to call back if they change their mind. End the screening interview.

1. **How old are you?** ______________ * must be between the ages of 18 and 35

2. **Are you right or left handed?** __________

   If LEFT HANDED thank the woman for her time, but she is not eligible. Remind her that she is welcome to contact the lab for future studies or to complete the online study.

3. **Are you currently using hormonal contraceptives?** YES NO

   If YES,

   2a) **What type?** ________________ * if IUD they are not eligible

   2b) **For how long?** ________________

**Do you mind answering some questions about your medical history to determine if you are eligible for the study?**

If YES → Explain that we need to ask these questions to determine their eligibility for the study. If they are still hesitant, ask them to think about it and call back.
4. Are you currently suffering from any medical or psychiatric conditions?

YES*   NO → go to #6

→ If yes, what condition(s) have you been diagnosed with?

______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________

→ Are you taking any medications for this/these conditions?   YES*      NO

→ If yes, which one(s)?

______________________________________________________________________________

→ Are you receiving any other treatment for this/these conditions?   YES*      NO

→ If yes, which one(s)?

______________________________________________________________________________

→ Have you previously taken any medication or received any other treatment for this/these conditions?   YES*      NO

→ If yes, which one(s)?

______________________________________________________________________________

5. Have you ever suffered, or are you currently suffering, from a chronic or recurrent pain condition (other than genital pain)?  Note: Chronic pain refers to persistent pain that often lasts for months (e.g., back pain). Recurrent pain refers to pain episodes that reoccur that are interspersed with pain-free episodes (e.g., migraine headaches).

YES*   NO → go to #6

→ If yes, what condition(s) have you been diagnosed with?

______________________________________________________________________________

→ When did this episode/these episodes occur?
→ How long did this episode/these episodes last?
______________________________________________________________________________
______________________________________________________________________________
_______________________________________________________

→ Are you currently taking painkillers for this/these conditions? YES* NO → go to #7

→ If yes, which one(s)?

6. When was your last gynecological examination?

→ Was it painful? YES NO

IF SHE HAS NEVER had a gynecological examination thank the woman for her time, but she is not eligible. Remind her that if she would like to participate after having a gynecological examination we’d be happy to have her call back.

7. Do you use tampons or any other kind of internal feminine hygiene product (e.g., Keeper/Diva Cup)?

YES NO

7b) Do you experience pain when you insert/remove tampons/product? YES NO

8. Have you ever given birth? YES NO → go to #9

→ If YES: How many children do you have? _____________________

→ Through what method/s of delivery?

A) Vaginal delivery: How many? _____

B) Caesarean-section: How many? _____

→ Are you currently breast-feeding? YES* NO

If YES, thank the woman for her time, but she is not eligible. Remind her that she is welcome to contact the lab for future studies or to complete the online study.
9. Is there any possibility that you might currently be pregnant?  YES* NO

   If YES, thank the woman for her time, but she is not eligible. Remind her that she is welcome to contact the lab for future studies or to complete the online study.

10. What was the start date of your last menstrual period? ______________________

11. Do you have any difficulty at all with vaginal penetration or insertion?  YES* NO

   \(\rightarrow\) go to #14

   \(\rightarrow\) If yes, please describe:

   ___________________________________________________________  __________________
   _____________________________________________________________________

12. Do you currently experience pain in your genital region?  YES NO

   YES: For how long have you had this pain? ________________ (min 6 months)
   \(\rightarrow\) Go to #13 and use present tense

   NO: Have you ever had recurrent and persistent genital pain?
   \(\rightarrow\) YES: Why do you no longer have the pain?____________________________
   \(\rightarrow\) Go to #13 and use past tense
   \(\rightarrow\) NO skip ahead to #18

**VULVAR PAIN WOMEN ONLY (Questions 13 to 17)**

13. In what situations do/did you feel the pain?
   A) It is always or almost always present
   B) During sexual intercourse or activities involving vaginal penetration: Which activities?
   C) It is always or almost always there and worsens during sexual intercourse/activities involving vaginal penetration: Which activities?
   D) Other:

   _____________________________________________________________________

   If B or C is endorsed: When does/did the pain START (or worsen) during sexual intercourse or activities involving vaginal penetration?
   A) When the penis/finger/object starts to enter the vagina
   B) When the penis/finger/object has fully entered and is thrusting*
   C) Only after penetration: How long does it last? ______________________
14. In which genital areas do/did you feel the pain?
   A) At the vaginal opening
   B) Everywhere on the vulva
   C) Inside the vagina
   D) In the pelvic or abdominal region*
   E) Other:

15. What adjective/s would you use to describe the pain you feel in your genital region?

16. Did you receive any diagnosis for this pain?  YES  NO → go to #17
   → If yes, what diagnosis/diagnoses did you receive?

   → By whom?

   → When?

17. Have you ever undergone any treatment for the pain?  YES  NO → go to #18
   → If yes, which one(s)?

   → Are you currently undergoing any treatment?  YES  NO
      → If yes, which one/s?
18. To determine whether you are eligible for the FMRI testing I am going to read out the FMRI safety checklist. Please indicate whether or not you have any of the following.

<table>
<thead>
<tr>
<th>Item</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneurysm clips (brain, abdominal, carotid)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac pacemaker, internal electrodes or wires</td>
<td></td>
<td></td>
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<tr>
<td>Internal defibrillator</td>
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<td></td>
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<tr>
<td>Prosthetic heart valve replacement</td>
<td></td>
<td></td>
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<tr>
<td>Electronic implant or device</td>
<td></td>
<td></td>
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<tr>
<td>Magnetically activated implant or device</td>
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<tr>
<td>Occupational history as a sheet metal worker, machinist, welder, etc</td>
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<td></td>
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<tr>
<td>History of metal fragments in the eye, head or body</td>
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<tr>
<td>Shrapnel or gunshot wound</td>
<td></td>
<td></td>
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<tr>
<td>Orbital/eye prosthesis, eyelid spring or wire</td>
<td></td>
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<tr>
<td>Cochlear, otologic or other ear implant</td>
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<tr>
<td>Any type of intravascular coil, filter or stent</td>
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<tr>
<td>Shunt (spinal or intraventricular)</td>
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<tr>
<td>Swan-Ganz or thermo dilution catheter</td>
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<tr>
<td>Implanted neurostimulator (spinal cord, bone, etc)</td>
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<tr>
<td>Vascular access port and/or catheter</td>
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<tr>
<td>Implanted drug infusion device (insulin, etc)</td>
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<td>Tattoo or permanent eyeliner</td>
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<tr>
<td>Body piercing * (removable is fine)</td>
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<tr>
<td>Radiation seeds or implants</td>
<td></td>
<td></td>
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<tr>
<td>Artificial or prosthetic limb</td>
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<tr>
<td>Joint replacement (hip, knee, etc)</td>
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<tr>
<td>Bone or joint pin, screw, nail, wire, plate, etc</td>
<td></td>
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<tr>
<td>Surgical staples, clips, metallic structures or wire mesh</td>
<td></td>
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<tr>
<td>Other implant</td>
<td></td>
<td></td>
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<tr>
<td>Breathing problem or motion disorder</td>
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<td></td>
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<tr>
<td>Dentures or partial plates</td>
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<tr>
<td>Hearing aid</td>
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<tr>
<td>Medication patch</td>
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<td></td>
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<tr>
<td>Claustrophobia</td>
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<tr>
<td>Are you pregnant or breast feeding?</td>
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<tr>
<td>Breast implants or tissue expanders</td>
<td></td>
<td></td>
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<tr>
<td>IUD, diaphragm or pessary</td>
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</table>
* If YES to any of the items on the list they may not be eligible for the study. Please tell them that you need to consult with your supervisor and will get back to them. *EXCEPTION is removable body piercings.

Initial Decision

NOT ELIGIBLE* _____ (If they are not eligible, explain to them why and thank them for their time. Suggest that they might be interested in another study.)

NOT SURE ____ (If not sure, tell them that you will call them back after discussing it with your supervisor.)

CONTROL GROUP _____† (Tell them that they are eligible for the study.)

VVS _____† (Tell them that they are eligible for this study.)

†Are you interested in participating in the study?  YES  NO  NOT SURE

→ If no/not sure, thank them for their time and ask them to call back if they change their minds. Answer any questions they might have, especially if they are not sure.

→ If yes, ask: Book the gynecological exam according to Dr. Chamberlain’s schedule.
   Gynecological Exam Date/time booked: _________________________________

→ What is the best way to contact you in order to confirm the appointment?
   NOTE: Inform them that if we leave a message, we would leave only our name and number and that we are calling from Queen's University.

Home: ____________________  Can we leave you a message? YES  NO

Work: ____________________  Can we leave you a message? YES  NO

Cell: _____________________  Can we leave you a message? YES  NO

Email address: ________________________________
Dear Participant,

Thank you very much for your participation in the fMRI study examining attention and pain processing in women with provoked vestibulodynia (PVD) and healthy controls. Your contribution to research is essential to progress in this field. For your time and inconvenience, you will be receiving your $100.00 cheque in the mail shortly. A package on PVD which includes useful information, tips, and resources has been included with this form. If you have any questions regarding the study or general information on PVD, please contact our lab at any time.

The Sexual Health Research Lab currently has a number of studies in progress examining areas such as: heterosexual and same-sex relationships, long distance relationships, genital pain conditions, sexual arousal, and sexual arousal disorders. Should you be interested in participating in any other studies, please do not hesitate to refer to the ongoing studies page on our website: http://psyc.queensu.ca/faculty/pukall/index.htm or contact us by phone (613) 533-3276 or email SHRL@queensu.ca.

Sincerely,

Katherine S. Sutton, MA
Appendix F

Letter of Information

Attention and Pain Processing: An fMRI Study

Investigators:
Katherine Sutton, MA, Department of Psychology, Queen’s University
Caroline F. Pukall, PhD, Department of Psychology, Queen's University
Susan Chamberlain, MD, Dept of Obstetrics and Gynecology, Kingston General Hospital

Purpose of the study
The purpose of this study is to investigate how your brain perceives pain. The current study will examine differences in pain processing between women with provoked vestibulodynia (PVD; a common cause of painful intercourse) and healthy control women. Measures of psychosocial functioning will also be examined to assess whether or not they are related to the experience of pain in terms of the unpleasantness and intensity of the pain.

Study procedures
Your participation in this study involves undergoing the following procedures: 1) a gynecological examination; 2) a semi-structured interview and the completion of questionnaires; and 3) a sensory testing and functional MRI (fMRI) session. The gynecological examination will take place at the Department of Obstetrics and Gynecology, Kingston General Hospital. The interview, questionnaires, and sensory testing session will take place at the Queen’s MRI Facility located in the Cancer Research Institute at 15 O’Kill Street (for directions please refer to their website: http://www.queensu.ca/neurosci/brain_facility.php).

Gynecological examination: During the gynecological examination (5-10 minutes), the doctor will visually and manually examine your internal and external genitalia and reproductive organs and will touch different areas of your vulva (i.e., external genitals) with a cotton-swab. The doctor will ask you to rate any pain you experience during this examination on a scale of 0 to 10. You will be in complete control of the procedure and may ask to stop at any time and/or control the speed of the examination. A research assistant will be, and a medical student may be, present during the examination.

Interview and questionnaires: The semi-structured interview and questionnaires will take approximately 45 minutes to complete and will cover sociodemographic information, gynecological and medical history, vulvar pain history, current physical and psychological symptoms, and sexual functioning.

Sensory testing session: During the sensory testing session, pressure stimuli of varying intensity (some non-painful and some painful) will be applied on your vulvar vestibule (i.e., the vaginal opening). This testing will be carried out by a trained graduate student (Kate Sutton, MA) who will touch these areas with a spring-based cotton-swab applicator. The touching lasts only a few seconds, after which you will be asked to rate the sensations on intensity and unpleasantness scales.
Although some of the stimuli in the sensory testing session may feel uncomfortable or painful to you, none will damage your skin. Also, you can withdraw from and terminate any stimulus that is too uncomfortable at any time.

**fMRI session:** During the fMRI session, pressure pain stimuli will be applied to your vulvar vestibule at a pressure determined during the sensory testing session. You will be asked to read word lists presented on a screen in front of you and to rate the painful sensations by looking at the ratings you choose. This portion of the testing will take approximately 1.5 hours and will consist of scanning both your brain and spinal cord.

**Compensation**
Upon completion of the gynecological examination, the interview/questionnaire session, and the sensory testing and fMRI sessions, you will receive $100.00 as compensation for your time and inconvenience. If the study has to be terminated for scientific reasons or if you decide to terminate the study, compensation will be adjusted according to the fraction of the study completed.

**Advantages of participating in this study**
The information obtained from this study will potentially help our understanding of the spinal and brain processes involved in the development and maintenance of PVD and, possibly, other related chronic pain conditions.

**Disadvantages of participating in this study**
The major disadvantage involved in participating in this study is that some of the above procedures (i.e., gynecological examination, and sensory testing and fMRI sessions) may be uncomfortable or painful. The pressure stimuli used during the sensory testing session are intended to cause pain, and may result in discomfort, and/or temporary reddening of the skin, but they will not damage your skin. In addition, as some of the questions asked as part of the interview/questionnaire part of the study may cover sensitive topics, such as anxiety and sexual functioning, you may experience some discomfort answering them. Remember that you are free to discontinue your participation at any point during the study without having to provide explanation.

**Confidential nature of this study**
Your participation in this study is strictly confidential. The investigators will take all reasonable measures to protect the confidentiality of your records. This includes replacing your name and any identifying information with coded numbers. There will be one password-protected file linking your name and contact information with your participant ID number; the password will be available only to the members of the research team working directly on this study. All written records and data will be identifiable only by your participant ID number, and all of this information will be kept in a locked filing cabinet. You will not be identified in any publication or reports of this research; data will be aggregated in all reports of this study.

**Discontinuation of this study**
You are under no obligation to participate in this study, and your acceptance or refusal will not affect access to services. Furthermore, you are free to withdraw from the study at any time, and you are free to refuse to answer any question posed without need of any explanation on your part. In addition, the investigators may end your participation in this study for purely scientific reasons at any time.
Appendix G

Consent form

I, __________________________________________, have volunteered to participate in the study entitled Attention and Pain Processing: An FMRI Study, conducted by Katherine Sutton, MA, and Drs. Caroline Pukall and Susan Chamberlain.

I consent to the information contained in the Letter of Information and understand what is required for participation in the study. I understand that I will undergo a gynecological examination that will take place at the Kingston General Hospital to determine what genital pain problem I have, or to ensure that I am pain-free and can participate in the study as a control participant. In addition, once a diagnosis is established, I understand that I will complete an interview and questionnaire session. I understand that some of the questions in this session may be quite personal in nature as some of them are related to topics such as anxiety or sexual functioning. Further, I understand that I will undergo a sensory testing session and functional magnetic resonance imaging (fMRI) which involve the application of non-painful and painful pressure stimuli to my vulvar vestibule (i.e., vaginal opening). I understand that the vulvar stimuli will be applied by a trained female graduate student who has obtained approval through a medical directive to perform the procedures in the current study. I understand that my participation in the study is completely voluntary and that I am free to withdraw at any time. I also understand that my confidentiality will be protected throughout the study, and that the information I provide will be available to researchers with scholarly interests in vulvodynia (i.e., chronic genital pain in women).

Should I have further questions, I understand that I can contact any of the following individuals:

- Dr. Caroline Pukall (533-3200; caroline.pukall@queensu.ca), Assistant Professor at the Department of Psychology at Queen's University and primary investigator of this study
- Dr. Kevin Munhall (533-2492; kevin.munhall@queensu.ca), Head of the Department of Psychology at Queen's University
- Dr. Albert Clark (533-6081; clarkaf@queensu.ca), Chair of the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board

Signature: __________________________________________

Date: __________________________________________
Information about Confidentiality

All information disclosed during your participation in this research study is confidential and will not be disclosed to anyone without your written and informed consent except where reporting is required by law, that is –

1. where there is suspicion that a child or children (that is, an individual who is PRESENTLY under the age of 16) has been or is being abused,

2. where the research participant is likely to harm herself or himself unless protective measures are taken,

3. where the research participant presents a serious danger of violence to others, and

4. if the research participant reveals that she has been sexually abused by a health care provider (for example, a psychologist or physician) covered by the Regulated Health Professionals Act, it is necessary by law to report the name of the perpetrator to his/her governing body.

IF YOU HAVE ANY CONCERNS ABOUT THESE MATTERS, OR ABOUT THIS FORM, PLEASE DISCUSS THESE WITH ME.

******************************************************************************************************
PLEASE SIGN THE ACKNOWLEDGEMENT BELOW TO INDICATE THAT YOU HAVE READ THIS INFORMATION ABOUT CONFIDENTIALITY
******************************************************************************************************

I acknowledge the circumstances that limit confidentiality and I accept them.

Participant’s name  Participant’s signature  Date

Witness’ name  Witness’ signature  Date

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Appendix H

Past Medical History

Age: _________      Weight: _________      Height: _______

Major illnesses & hospitalizations

Cardiovascular/vascular (e.g., angina, heart attack, transient ischemic attack, stroke, etc)

______________________________________________________________________________

Respiratory (e.g., asthma, chronic obstructive pulmonary disease, emphysema, etc)

______________________________________________________________________________

Gastrointestinal/renal (e.g., irritable bowel syndrome, interstitial cystitis, etc)

______________________________________________________________________________

Musculoskeletal/rheumatological (e.g., fibromyalgia, arthritis, etc)

______________________________________________________________________________

Endocrinological (e.g., hypothyroidism, diabetes, etc)

______________________________________________________________________________

Gynecological (e.g., endometriosis, pelvic inflammatory disease, recurrent yeast infections, etc)

______________________________________________________________________________

Psychiatric/psychological (e.g., depression)

______________________________________________________________________________

Past surgeries

______________________________________________________________________________

Reproductive history

Number of pregnancies: __________

Number of live births: _____________

Mode of delivery: ___________________________________________________

Pregnancy complications: _____________________________________________

Sexually transmitted infections (e.g., Chlamydia, gonorrhea, herpes, HPV)

______________________________________________________________________________

Current medications

______________________________________________________________________________

Allergies

______________________________________________________________________________

Other:

______________________________________________________________________________
Appendix I

MEDICAL DIRECTIVE

Sensory Testing of the Vulvar Region in Women With and Without Vulvodynia and Sexual Dysfunction

Background: This medical directive has been created to provide approval to the supervisor (Caroline Pukall, PhD, Department of Psychology, Queen's University) and graduate students of the Sexual Health Research Lab (SHRL) to carry out a variety of sensory testing procedures in the vulvar region for research purposes. The studies are directly supervised by Caroline Pukall, and they will be conducted at the SHRL where the appropriate equipment is located (e.g., quantitative sensory testing equipment) or at another relevant location (e.g., MRI Facility, Center for Neuroscience Studies, Queen's University). The research studies focus on women with vulvar pain (i.e., vulvodynia) and sexual dysfunction. Currently, study recruitment is targeted for women with vulvodynia, including vulvar vestibulitis syndrome and generalized vulvodynia, and women with female sexual arousal disorder (FSAD). In addition, healthy women are also recruited as a comparison group. Dr. Susan Chamberlain (Department of Obstetrics and Gynecology, Kingston General Hospital) will physically examine potential participants to determine their eligibility and diagnosis. Dr. Chamberlain is actively involved in the ethics and research protocols for these studies.

Authorizing Physician: Dr. Susan Chamberlain M.D.

To: Dr. Pukall and the graduate students in the Sexual Health Research Laboratory, Department of Psychology, Queen's University who have been trained in genital sensory testing by Dr. Pukall and have obtained Departmental Assistant status for Kingston General Hospital.

Clinical Conditions Required:

- Female participants
- Symptoms consistent with vulvodynia or sexual dysfunction, or control women with no symptoms of vulvodynia or sexual dysfunction

Situational Conditions Required:

- Informed consent from each participant

Contraindications: Sensory testing and imaging will not be carried out if participants meet any of the following criteria:

- Have a major medical, psychiatric, or pain (other than vulvar pain) disorder that significantly interferes with daily or sexual functioning
- Use pharmacological agents that interfere with pain processing
- Are currently pregnant, breastfeeding, or within six months postpartum

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Appendix J

GYNECOLOGICAL EXAMINATION

Participant ID Number: _______________ Date: ________________
Examing physician: _______________ Research Assistant: ________________

SECTION I: INSPECTION OF THE VULVA

**Clitoris**
- No abnormalities
- Partially hooded
- Complete phimosis

**Labia minora**
- No abnormalities
- Partially fused
- Completely fused

**Posterior fourchette**
- No abnormalities
- Scar from previous fissure
- Active fissure

**Vestibule: BEFORE the cotton-swab test**
- No abnormalities
- Erythema
- Fissure
- Synechia

**Pubic Hair**
- Sparse
- Normal
- Shaved

**Labia**
- Dry, atrophic
- In between atrophic and full
- Full

SECTION II: COTTON-SWAB TEST

**LABIA MAJORA: pain intensity ratings**
- Patient’s right, anterior: ______
- Patient’s left, anterior: ______
- Patient’s right, mid-point: ______
- Patient’s left, mid-point: ______
- Patient’s right, posterior: ______
- Patient’s left, posterior: ______

**INNER LABIA MINORA: pain intensity ratings**
- Patient’s right, anterior: ______
- Patient’s left, anterior: ______
- Patient’s right, posterior: ______
- Patient’s left, posterior: ______
**MIDLINE AREAS and VESTIBULE (random order): pain intensity ratings**

Between vagina and urethra: ______  
1 o’clock: ______  
Inside vagina: ______  
4-5 o’clock: ______  
Posterior fourchette: ______  
6 o’clock: ______  
Perineum: ______  
7-8 o’clock: ______  
11 o’clock: ______

**Appearance of vestibule after cotton-swab test:**

<table>
<thead>
<tr>
<th>No erythema</th>
<th>Erythema</th>
<th>Other</th>
</tr>
</thead>
</table>

Ask women with provoked pain during sexual activity only:

Does this pain feel like the pain you experience during sexual activity?  
Yes  No  Maybe  
If no, how was it different? _____________________________  
_______________________________________________

**ANAL WINK TEST**

<table>
<thead>
<tr>
<th>Present</th>
<th>Weak</th>
<th>Absent</th>
</tr>
</thead>
</table>

**SECTION III: MUSCLE TENSION ASSESSMENT (random order)**

Apply pressure inside the vagina for 3 seconds at 8, 6, and 4 o’clock. Record pain intensity ratings.

8 o’clock: ______  
6 o’clock: ______  
4 o’clock: ______

**Evaluation of muscle tension by the examining physician**

<table>
<thead>
<tr>
<th>Relaxed</th>
<th>Tense</th>
<th>Severe tension</th>
</tr>
</thead>
</table>

**Kegel evaluation: degree of contraction**

<table>
<thead>
<tr>
<th>None</th>
<th>Weak</th>
<th>Strong</th>
<th>Very strong</th>
</tr>
</thead>
</table>

**Kegel evaluation: degree of relaxation**

<table>
<thead>
<tr>
<th>None</th>
<th>Relaxed</th>
<th>Tense</th>
</tr>
</thead>
</table>
SECTION IV: SPECULUM EXAMINATION

Speculum insertion: pain intensity rating ______

Skin elasticity and turgor:

<table>
<thead>
<tr>
<th>Poor</th>
<th>Fair</th>
<th>No abnormalities</th>
</tr>
</thead>
</table>

Vaginal mucosa:

| Atrophic | No abnormalities, rugal appearance |

Vaginal depth:

| Shortened | No abnormalities |

SECTION V: BIMANUAL PALPATION

Palpate the uterus, the adnexae, and the cervix. Describe any and all abnormalities, including pain (fibroids, cysts, endometriosis, etc):


Introitus:

| <1 fingerbreadth | 1 fingerbreadth | 2 fingerbreadths | +2 fingerbreadths |

SECTION VI: OVERALL UNPLEASANTNESS OF GYNECOLOGICAL EXAMINATION

Ask: On a scale from 0 to 10, how unpleasant overall was the gynecological examination? _____

SECTION VII: DIAGNOSTIC IMPRESSION

<table>
<thead>
<tr>
<th>No gynecological diagnosis</th>
<th>Lichen planus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vulvar vestibulitis syndrome</td>
<td>Lichen sclerosus</td>
</tr>
<tr>
<td>Generalized vulvodynia</td>
<td>Heightened muscle tension</td>
</tr>
<tr>
<td>Vaginal atrophy</td>
<td>Other _____ please specify: _______</td>
</tr>
<tr>
<td>Vulvar fissures</td>
<td></td>
</tr>
</tbody>
</table>

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Appendix K

Mons veneris
Clitoral hood (prepuce)
Clitoris
Vestibule
Perineum
Anus

Labia majora
Labia minora
Urethral opening
Introitus

(a)

© 2005 Wadsworth - Thomson
Appendix L

Structured Interview

PART A: Socio-Demographic Information

1) Date of birth _______/_______/_______   Age: __________
   mo       day       year

2) Place of birth ____________________________

2b) If not Canada, number of years residing in Canada: _____

3) What culture do you see yourself as most associated with? ______________________

4) What is your native tongue?
   1) English
   2) French
   3) Other (please specify:______________)

5) In what religion were you brought up? _______________________

6) How many years of schooling do you have post high school? _____________

7) What is the approximate total annual income of your household (include parents if in undergrad)?

   1) $ 0 - $9,999  4) $30,000 - $39,999  7) $60,000 – $74,999
   2) $10,000 - $19,999  5) $40,000 - $49,999  8) $75,000 – $99,999
   3) $20,000 - $29,999  6) $50,000 - $59,999  9) $100,000 +

PART B: Relationship History

1) Which of the following best describes your sexual orientation?

   1) heterosexual
   2) homosexual
   3) bisexual
   4) hetero-flexible
   5) not sure
2) Which of the following best describes your current situation?

1) not dating at the moment  
2) no regular partner at the moment  
3) dating one partner regularly  
4) living with a partner  
5) married

3) How long have you been in this situation? ________ years ________ months

4) How old were you when you had intercourse for the first time? ________ years old.

5) Do you remember it as being painful? 1) YES  2) NO (N/A for #6)

→ if yes, describe

________________________________________________________________________
________________________________________________________________________

→ if no, go to #7

6) On a scale of 0 to 10, please rate the intensity of the pain you experienced during your first intercourse. _____ N/A

7) Do you remember it as being unpleasant? 1) YES  2) NO (N/A for #8)

→ if no, go to #9

8) On a scale of 0 to 10, please rate the degree of unpleasantness you experienced during your first intercourse. _____ N/A

9) What is the total number of partners you have had intercourse with (including one-night stands)? ________

   How many of these were one night stands? ________

   How many of these were short term? ________

   How many of these were long term (i.e., longer than three months)? ________

10) How many long term (i.e., longer than three months) relationships have you been in? ________

   ➢ How many of the long-term relationships reported above have you been in since your vulvar pain (i.e., genital pain) started? ________
11) How many casual dating (i.e., relationships that you did not consider yourself committed to) relationships have you been in? _______

➤ How many of the dating relationships reported above have you been in since your vulvar/genital pain started? _______

12) Were you in a relationship at the time that your vulvar/genital pain started?

Yes _________  No _________

➤ If yes, how long had you been in the relationship before the pain first started? _______________

➤ If yes, and if you are no longer in this relationship, for how long were you in the relationship after the pain started? __________

13) How has your relationship status changed since the onset of your vulvar/genital pain?

________________________________________________________________________

PART C: Gynecological and Medical History

1) Do you menstruate regularly (approximately once a month)?  1) YES  2) NO

If no, why not? _________________________________

2) What was the start date of your last menstrual period? _______ / _______ / _______

[ coding:  1) Follicular (few days after menstruation)  
2) Ovulatory (about 2 weeks after start of last menstruation)  
3) Luteal (after ovulation, few days before menstrual onset)  
4) Menstrual]

3) On a scale of 0 to 10, please rate the intensity of the pain you experience during your menstrual periods (over the last year). _____  N/A

4) On a scale of 0 to 10, please rate the degree of unpleasantness you experience during your menstrual periods (over the last year). _____  N/A

5) If has current partner: Do you and/or your partner use any method(s) of contraception?

1) YES  2) NO
If no current partner: Did you and/or your past partners use any method(s) of contraception?
1) YES  2) NO  3) DEPENDENT ON WHICH PARTNER

If no to either question, why not? ______________________________________

If yes to either question, which one(s)? ____________________________________

If using the pill, which brand? __________________________
   How long have you been using the pill? __________________________

6) How many yeast infections have you had? ________________
   → if 0, go to # 9, and N/A for # 7 and 8.

7) Have you suffered from repeated yeast infections?  1) YES  2) NO  3) DK  4) N/A
   → If yes, since what age? ________________

8) How were the yeast infections diagnosed?
   N/A
   1) clinical plus positive culture: Number of times ______
   2) clinical only: Number of times ______
   3) self-diagnosed: Number of times ______

9) What gynecological problems have you had?

1) Chlamydia ______  2) Gardnerella vaginalis ______
3) Genital herpes ______  4) HPV/Genital warts ______
5) Gonorrhea ______  6) H.I.V. ______
7) Syphilis ______  8) Trichomoniasis ______
9) Bladder/urinary infections ______  10) Interstitial cystitis ______
11) P.I.D. ______  12) Endometriosis ______
13) Other (please specify: ___________)  14) None ______

10) What kind of gynecological interventions have you had?

1) Hysterectomy ______  2) Laparoscopy ______
3) Ovariectomy ______  4) Tubal ligation ______
5) C & T ______  6) Abortion ______
7) Other (please specify: ____________)  8) None ______

11) Have you ever been diagnosed with any chronic pain condition?
   1) YES  2) NO
   If yes, what condition(s)? ______________________________________

12) Are you currently taking any analgesics?  1) YES  2) NO
   If yes, why? ______________________________________
   For how long? ______________________________________
13) Are you currently taking any medications?  
1) YES  2) NO
If yes, why? __________________________________________________________
For how long? ________________________________________________________

14) How much bodily pain have you had during the past 4 weeks?

1) None ____  2) Very mild ____  
3) Mild ____  4) Moderate ____  
5) Severe ____  6) Very severe ____

15) During the past 4 weeks, how much did bodily pain interfere with your work, including both
work outside the home and housework?

1) Not at all ____  2) A little bit ____  
3) Moderately ____  4) Quite a bit ____  
5) Extremely ____

16) Do you regularly (i.e., once a month or more) suffer from pain/discomfort in any of the
following body sites or have any of the following problems?

→ for each “yes” response, ask: a) How serious of a problem is this for you?  
(0 = not at all serious, 5 = moderately serious, 10 = extremely serious)

→ and How much does this pain/discomfort interfere with your usual activities?  
(0 = not at all, 5 = moderately, 10 = totally)

→ and How often do you find yourself thinking and/or worrying about the pain?  
(0 = not at all, 5 = some of the time, 10 = all of the time)

<table>
<thead>
<tr>
<th>Body Area (indicate if yes)</th>
<th>Seriousness (0 – 10)</th>
<th>Interference (0 – 10)</th>
<th>Rumination (0 – 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Face (jaw, eyes, ears)</td>
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<td></td>
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<tr>
<td>Mouth (teeth, gums, etc)</td>
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<tr>
<td>Neck</td>
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<tr>
<td>Throat</td>
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<td></td>
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<tr>
<td>Back</td>
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<td></td>
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<tr>
<td>Arms</td>
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<td></td>
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<tr>
<td>Hands</td>
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<tr>
<td>Chest</td>
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<tr>
<td>Breast</td>
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<td></td>
<td></td>
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<tr>
<td>Menstrual cramps</td>
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<tr>
<td>Stomach/abdomen</td>
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<td></td>
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</tr>
<tr>
<td>Pelvic area</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

228
<table>
<thead>
<tr>
<th>Pain Location</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td></td>
<td></td>
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<tr>
<td>Kidney</td>
<td></td>
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<tr>
<td>Ovary/ovulatory pain</td>
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<tr>
<td>Uterus</td>
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<tr>
<td>Endometriosis</td>
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<tr>
<td>Cystitis</td>
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<td></td>
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<tr>
<td>Yeast infections</td>
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<tr>
<td>Vaginal infections</td>
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<tr>
<td>UTIs</td>
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<td></td>
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<tr>
<td>Gall bladder</td>
<td></td>
<td></td>
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<tr>
<td>Legs</td>
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<td></td>
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<tr>
<td>Feet</td>
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<td></td>
</tr>
<tr>
<td>Joints</td>
<td>(specify</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibromyalgia</td>
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<td></td>
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<tr>
<td>Chronic fatigue syndrome</td>
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<td></td>
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<tr>
<td>Arthritis</td>
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<td></td>
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<tr>
<td>Angina</td>
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<td></td>
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<tr>
<td>Osteoporosis</td>
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<td></td>
<td></td>
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<tr>
<td>Burns</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Scars</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms/pain</td>
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<td></td>
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</tr>
<tr>
<td>Neuralgia</td>
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<tr>
<td>Colitis/Crohn’s disease/IBS</td>
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</tr>
<tr>
<td>Rectum</td>
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<td></td>
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<tr>
<td>Hemorrhoids</td>
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<td></td>
<td></td>
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<tr>
<td>Constipation</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Indigestion</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

17) If more than one pain was chosen, which is the worst? _____ N/A

18) On a scale of 0 to 10, please rate the intensity of this/the worst pain. _____ N/A

19) On a scale of 0 to 10, please rate the degree of unpleasantness you experience during this/the worst pain. _____ N/A
PART F: Sexual Activity

1) Over the past 6 months, approximately how many times have you attempted intercourse per month? _____________

**If NOT presently having intercourse please move to PART H

1b) Are you happy with this frequency of intercourse? YES NO Not Sure

→ If no or not sure, would you like intercourse to be less or more frequent? __________

Why do you suppose that the actual frequency of intercourse does not match your desired frequency?

______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________

2) How many of these times did you initiate intercourse? ______

3) On a scale of 0 to 10, with 0 representing no confidence and 10 representing complete confidence, how confident do/did you feel initiating intercourse with your partner(s)? ______

Please explain why you chose that rating in terms of initiating intercourse.

______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________

4) On a scale of 0 to 10, with 0 representing no confidence and 10 representing complete confidence, how confident do/did you feel engaging in intercourse with your partner(s)? ______

Please explain why you chose that rating in terms of engaging intercourse.

______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________

5) Typically, what percentage of foreplay occasions lead to intercourse? _______

→ Are you happy with this situation? YES NO Not Sure

Why/Why Not?

______________________________________________________________________________
______________________________________________________________________________
______________________________________________________________________________
6) Are you currently engaging in any of the following sexual activities? If so, do any of them cause you pain?

1) Deep kissing
2) Non-genital touching
3) Touching of partner’s genitals
4) Partner touching your genitals
5) Giving oral sex
6) Receiving oral sex
7) Anal play/sex on partner
8) Anal play/sex on you
9) Other (Explain): __________________________________________________
________________________________________________________________________
________________________________________________________________________

7) Do you presently experience, or have you ever experienced, recurrent and persistent pain during intercourse? ________________________________

7b) Even if you have pain free intercourse most of the time, typically what percentage of the time over the past 6 months has intercourse been painful? _________

**IF the woman is in the PVD group continue to Part G

PART G: Pain with Intercourse History (PVD ONLY)

1) When did you first start experiencing pain with intercourse?

_______month _______year

2) How did it start?

1) with first experience
2) after repeated yeast infections
3) after childbirth
4) for no apparent reason
5) change of partner
6) after repeated bladder infections (UTI’s)
7) with onset of menopause
8) after gynecological surgery (please specify: __________________________)
9) life stress (e.g., marital conflict, financial problems; specify: ______________)
10) after an abortion
11) Other (please specify:____________________________________________)

3) How many health professionals have you consulted for the pain? ______________

→ What types of health professionals were consulted? __________________________
________________________________________________________________________
________________________________________________________________________
4) What diagnoses and treatments were you given by the health professionals to whom you reported the pain? None given

Please list the name of every diagnosis; medication/treatment you remember receiving and the number of times you took/underwent the prescribed treatment.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Number of times taken</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1) &lt;10 2) &gt;10 3) DK</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1) &lt;10 2) &gt;10 3) DK</td>
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<td>1) &lt;10 2) &gt;10 3) DK</td>
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<td></td>
<td></td>
<td>1) &lt;10 2) &gt;10 3) DK</td>
</tr>
</tbody>
</table>

5) Have you ever attempted to treat or alleviate the pain? NO YES

→ If yes, how?

1) Changing aspects of sex life (e.g., position, speed, enhancing arousal)
2) Creams (e.g., K-Y, Crisco, moisturizers, corticosteroids, hormonal, anesthetics)
3) Alternative medicine (e.g., vitamins, diets, homeopathic remedies, physiotherapy)
4) Psychological treatments (e.g., psychotherapy, hypnosis, Kegels, biofeedback)
5) Surgery (e.g., vestibulectomy, laser, D&C)
6) Other medical treatments (e.g., hormones, interferon, antibiotics)
7) Small changes (e.g., cotton underwear, mild soaps, changing mattresses)
8) Other (please specify: ____________________________________________)

6) When does the pain typically start?

1) before the penis touches the vaginal opening; it is always there
2) when the penis starts to enter the vagina
3) when the penis has fully entered and is thrusting
4) after intercourse (how long does it last? _____________________________)
5) Other (please specify: ____________________________________________)

7) How long does the pain typically last?

1) during penile entry only
2) during penile thrusting only
3) only for a period after penile exit
4) during penile entry and after penile exit
5) during penile entry and during penile thrusting
6) during penile thrusting and for some time after penile exit
7) during penile entry, during penile thrusting, and after penile exit
8) it is never the same: there is no typical pattern

If it lasts after penile exit, please state for how long after the pain is felt.

Time: _____ minutes _____ hours _____ days

8) Where do you typically feel the pain during intercourse? Is there a specific spot you can show me? If yes, where? (show vulva diagram)

1) at the vaginal opening
2) everywhere on the vulva
3) inside the vagina

9) If chose only one location, proceed to correct #. If more than one pain, can you differentiate among these different pains?

1) YES 2) NO 3) DK
→ If yes, or don’t know, continue to the appropriate #
→ If no, proceed to # 18

10) On a scale of 0 to 10, please rate the average intensity and unpleasantness of the pain at the:

- vaginal opening (past 6 months). _____ _____ N/A
- everywhere on the vulva (past 6 months). _____ _____ N/A
- inside the vagina (past 6 months). _____ _____ N/A

11) On a scale of 0 to 10, please rate the average intensity of pain you experience during intercourse. _____

12) On a scale of 0 to 10, please rate average degree of unpleasantness you experience during intercourse. _____

→ Administer psychosocial measures
Appendix M
## Appendix N

<table>
<thead>
<tr>
<th>Pain Words</th>
<th>Neutral Words</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharp</td>
<td>Solid</td>
</tr>
<tr>
<td>Cutting</td>
<td>Curious</td>
</tr>
<tr>
<td>Burning</td>
<td>Bashful</td>
</tr>
<tr>
<td>Tearing</td>
<td>Typical</td>
</tr>
<tr>
<td>Stabbing</td>
<td>Skillful</td>
</tr>
<tr>
<td>Unbearable</td>
<td>Unsuitable</td>
</tr>
</tbody>
</table>
Appendix O

Hemodynamic Response

0-1s → 1-2s → 2-5s → 5-10s → 10s
+3/5/7s

word → pressure → rest → rating scale → ISI
Appendix P

Statistical analysis: Design

Parameter estimability

Design description...

- Basis functions: hrf
- Number of sessions: 2
- Trials per session: 10 10
- Interscan interval: 2.00 (s)
- High pass Filter: Cut-off: 128 (s)
- Global calculation: mean voxel value
- Grand mean scaling: session specific
- Global normalisation: None
Appendix Q

function [picture_presentation, time_record, vocal_prompt] = slideshow2

working_dir = 'C:\MATLAB7\work\spm5\fMRI stimulus for matlab.ppt\';
output_dir = 'C:\MATLAB7\work\spm5\fMRI stimulus for matlab.ppt\';

cd(working_dir)

scrsz = get(0,'ScreenSize');
figure('Position',[1 scrsz(4) scrsz(3) scrsz(4)], 'MenuBar', 'none', 'ToolBar', 'none')
imshow('slide21.jpg', 'notruesize'), drawnow  % put up a "ready" screen

nbblocks = 18;
npics = 18;
picture_list = 1:npics;
picture_presentation = picture_list(randperm(length(picture_list)));

delays = [1*ones(1,6) 3*ones(1,6) 5*ones(1,6)];
ndelay = length(delays);
delay_list = delays(randperm(ndelay));

timeelapsed = 0;

c1 = find(picture_presentation <= 6);        % find the neutral conditions

% find the pain conditions

c2 = find( (picture_presentation <= 12)  &  (picture_presentation > 6) );
c3 = find(picture_presentation > 12);       % find the pseudo-word conditions

prompt_list = [1 1 2 2 3 3];              % 1=pain 2=neutral 3 = none
prompt_list1 = prompt_list(randperm(6));  % now randomize them, within each condition
prompt_list2 = prompt_list(randperm(6));
prompt_list3 = prompt_list(randperm(6));

vocal_prompt = zeros(1,nblocks);   % put the total list together
vocal_prompt(c1) = prompt_list1;
vocal_prompt(c2) = prompt_list2;
vocal_prompt(c3) = prompt_list3;

load('slideshowvocals.mat');

pause(2)
KbWait   %  wait for the signal to go

tic  % get ready to keep track of time
for n = 1:nbblocks
    time_record(n,1) = toc;

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vocal_num = vocal_prompt(n);
switch vocal_num
    case 1, vocal = Pain;
    case 2, vocal = Touch;
    case 3, vocal = None;
end
wavplay(vocal,Fs,'async')
pause(3)
picture_name = ['slide' num2str(picture_presentation(n)) '.jpg']
imshow(picture_name, 'notruesize'), drawnow
pause(2)
imshow('slide21.jpg','notruesize'), drawnow
time_record(n,2) = toc;
pause(8)
imshow('slide21.jpg','notruesize'), drawnow
pause(2)
imshow('slide19.jpg','notruesize'), drawnow  % change this later to the other fixation point
pause(2)
imshow('slide20.jpg'), drawnow
time_record(n,3) = toc;
pause(8)
imshow('slide21.jpg'), drawnow
pause(delay_list(n))
time_record(n,4) = toc;
end

imshow('slide21.jpg', 'notruesize'), drawnow  % put up a "you are done" screen

output_name = [output_dir 'slideshow_data_' datestr(now) '.mat'];
c = strfind(output_name, ':');
output_name(c(2:end)) = '_';
save(output_name, 'picture_presentation', 'time_record', 'vocal_prompt')
### Appendix R

#### Whole Sample Correlations Amongst Anxiety Measures.

<table>
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<tr>
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<th>STAI_T</th>
<th>PCS(v)</th>
<th>PCS</th>
<th>PASS(v)</th>
<th>PASS</th>
<th>ASI</th>
<th>PVAQ(v)</th>
<th>PVAQ</th>
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<td><strong>STAI_T</strong></td>
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<td>.675**</td>
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<td>.000</td>
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<td>.622**</td>
<td>.662**</td>
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<td>.000</td>
<td>.000</td>
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</tr>
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</table>

(v) = PVD group vulvar pain was compared with control group worst regularly experienced pain.