Psychological, Somatosensory and Autonomic Functions in Women suffering from Eating Disorders.

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Psychological, Somatosensory and Autonomic functions in Women suffering from Eating Disorders

General health and psychological, somatosensory and autonomic function were investigated in a sample of 23 eating disorder (ED) women currently in treatment and 16 controls. Somatosensory function in ED patients was generally similar to controls on cutaneous punctate sensitivity, pain sensitivity (i.e. pressure pain thresholds (PPT) on the hand or on soft tissues over the body, ischemic pain threshold and tolerance; pain distress and sensory ratings and reports of bodily aches and pains). The only differences were that bulimia nervosa (n= 6) was associated with elevated PPT on the hand and ED patient groups reported abdominal pain, and headaches for those with purging symptoms. Hand PPT correlated with BMIs (r = 0.34) and exercise frequency (r = 0.44). Self-reported general physical health and autonomic reactivity in ED patients (i.e., blood pressure, heart rate, heart rate variability, sympatico-vagal balance and sympathetically-driven stress-response) were similar to controls, with no major impairments of autonomic function in ED patients. Minor autonomic disturbances were lower blood pressure and slower heart rate in Anorexia Nervosa patients (AN), a slightly reduced stress-response in AN-Restrictive patients (n = 7) and a minor sympatico-vagal imbalance in AN-Binge/Purge patients (n = 10). On the other hand, ED patients, in particular AN Binge/Purge patients, suffered from various psychological impairments. Anxiety and Depression were related to autonomic function and to the inflammatory response to capsaicin across patients and controls. The results support the presence of clusters within ED subtypes which are associated with different profiles of general health, psychopathologies and somatosensory sensitivity, suggesting that treatment strategies also need to be specific.

Fonctionnement psychologique, somatosensoriel et autonomique chez des femmes souffrant de troubles alimentaires.

La santé générale et les fonctions psychologiques, somatosensorielles et autonomiques on été investiguées dans un échantillon de 23 femmes souffrant de troubles de l'alimentation (TA) sous traitement et 16 femmes sans TA. Les fonctions somatosensorielles des patients avec TA étaient, en général, similaires aux femmes sans TA pour la sensibilité ponctuée cutanée, la sensibilité à la douleur (i.e. seuil de douleur à la pression (SDP) sur la main ou sur les tissues mous du corps, seuil de douleur et tolérance ischémique, évaluation sensorielle et émotionnelle de la douleur et maux et douleurs allégués). Les seules différences étaient une association entre la Boulimie Nerveuse (BN) et une élévation du SDP sur la main, la présence de douleurs abdominales chez les patientes avec un TA, et de maux de tête chez les patients avec des symptômes purgatifs. L'indice de masse corporel (IMC) et la fréquence de l'activité physique étaient tous deux corrélés avec le SDP sur la main. L'autoévaluation de la santé physique générale et de la réactivité autonomique chez les patients souffrant d'un TA (i.e. Pression sanguine, pouls, variation des battements cardiaques, équilibre sympatico-vagual et réaction au stress induite par le système sympathique) étaient similaire à celles des femmes sans TA. Les troubles mineurs du système autonomique comprennent une baisse de la pression artérielle et des battements cardiaques chez les patients avec Anorexie Nerveuse (AN), une réduction mineure de la réponse au stress chez les patientes souffrant d'AN de type Restrictive (n =7) et un déséquilibre sympatico-vagual mineur chez les patientes souffrant d'AN de type boulimie/purgation (n =10). D'autre part, les patientes atteintes de TA, en particulier les patientes atteintes d'AN de type boulimie/purgation, souffrent d'une variété d'atteintes psychologiques. Les données indiquent une relation entre la dépression et l'anxiété et les fonctions autonomiques et l'inflammation au capsaicin chez les patients atteintes de TA et chez les femmes sans TA. Nos résultats supportent la présence de plusieurs regroupements à l'intérieur des sous-types de TA qui sont associés à des profiles différents de santé générale, de psychopathologies et de sensibilité sensorielle, suggérant que les stratégies de traitement devraient également être spécifiques.

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LIST OF ABBREVIATIONS

AN	Anorexia Nervosa
AN-B/P	Anorexia Nervosa with Binge/Purge Subtype
AN-R	Anorexia Nervosa with Restrictive Subtype
ANOVA	Analysis of Variance
BMI	Body Mass Index
BN	Bulimia Nervosa
DSM-IV	Diagnostic and Statistical Manual of the American Psychiatric Association
ED	Eating Disorder
ED50	Median Effective Dose
EDE-I	Eating Disorder Examination Interview
HADS	Hospital Anxiety and Depression Scale
Kg	Kilograms
Mg	Milligrams
Ml	Milliliters
PPT	Pressure Pain Threshold
PTT	Punctate Tactile Threshold
SCL-90-R	Symptom Checklist 90 Revised
SF-36	Short Form Health Survey

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CHAPTER 1

INTRODUCTION

Bulimia Nervosa (BN) and Anorexia Nervosa (AN) are chronic eating disorders (ED) of unknown origin associated with serious medical complications. Patients with ED are characterized by an intense fear of gaining weight and recurrent attempts to lose weight by means of self-starvation and/or purging behaviours. Several endocrine, metabolic, thermoregulatory and cardiovascular abnormalities have been identified in patients with eating disorders and comorbid depression and/or anxiety disorders are often observed. There is also evidence of disturbances in pain sensitivity in patients suffering from eating disorders, with the majority of studies suggesting that pain sensitivity is reduced. A variety of mechanisms (i.e. altered endogenous opioid activity, polyneuropathy, vagal afferent activation, etc.) have been hypothesized to underlie the alterations in pain sensitivity but, to our knowledge, none of these have been substantiated.

In the present study, general health, somatosensory and autonomic functions were studied in a sample of women suffering from AN and BN, in order to determine if disturbances in these systems might be related to the reduced pain sensitivity observed in the majority of patients with eating disorders. The measures that were used are justified by the fact that 1) the pain sensitivity abnormalities observed in eating disorder patients might be consequent to a general sensory dysfunction; 2) only three studies tested for pain tolerance in eating disorder patients(Girdler & al., 1998; Raymond & al., 1999a; Stein & al., 2003); 3) no studies have, to our knowledge, ever used more than 2 methods (e.g. heat pain and pressure pain) to measure pain threshold in eating disorder patients with the majority of them using only one method and 4) the current data on tactile threshold (ability to detect innocuous stimulation of the skin) is inconsistent. The autonomic measures are because patients with eating disorders are characterized by autonomic disturbances and the activity of the autonomic nervous system has been shown to affect pain sensitivity for both experimental and clinical pain.

This study's aim is twofold: (1) contribute to the understanding of the underlying mechanisms responsible for the alterations in pain thresholds in patients with eating disorders and (2) systematically evaluate possible covariates that could account for the fact that the alterations in pain threshold are not homogeneous across the eating disorder patient population; that is, some patients display higher levels of disturbances in their pain thresholds than others.

This study addresses five specific questions:

1. Are the increased pain threshold abnormalities accompanied by alterations in tactile[1] functions?
2. Is the pain threshold disturbance different for bulimia nervosa and anorexia nervosa?
3. Are specific behaviours (e.g. vomiting) or specific characteristics (e.g. perfectionism, low BMI) associated with the elevated pain thresholds?
4. Does the correlation between skin temperature and pain threshold that previous studies have found in patients with anorexia nervosa reflect an underlying relationship between autonomic function and pain sensitivity?
5. Is there a correlation between binging/purging behaviours and pain thresholds in patients with bulimia nervosa as previous studies suggested?
6.

The following thesis contains in its first section a brief description of AN and BN and their associated physiologic disturbances. Pain, comorbid disorders and previous studies assessing pain thresholds in patients with EDs are also discussed in this section. In the second part, possible mechanisms that could account for the abnormal pain thresholds observed in patients with eating disorders, particularly insensitivity to pain, are discussed and the variables that were measured are outlined. Then, the methods and procedures that were used are described. Finally, results are described and discussed and conclusions are drawn.

[1] Tactile refers to the sensitivity to light touch

1.1 Eating disorders and associated physiologic disturbances

Bulimia Nervosa (BN) and Anorexia Nervosa (AN) are chronic eating disorders (ED) that are both associated with severe, life-threatening physiological disturbances. BN is characterised by a negative self-evaluation based on body shape and weight, and recurrent episodes of binge eating where the patient eats abnormally large amounts of food, feels a loss of control, and makes inappropriate attempts to prevent weight gain (DSM-IV, 1994; Tapia, 1996). AN is characterised by extreme weight loss, intense fear of weight gain, body perception disturbances and amenorrhea. (DSM-IV, 1994; Tapia, 1996)

The endocrine and the autonomic systems are seriously compromised in patients with EDs. These systems work in unison, utilizing many interrelated regulatory and feedback mechanisms to maintain homeostasis[2]. As a result of recurrent starvation and/or binge-eating/purging episodes, the autonomic and endocrine systems are forced to undergo massive adaptations, causing many physiologic disturbances. Interestingly, many theorists argue that some of autonomic and endocrine abnormalities might have been present prior to the onset of the ED, suggesting these abnormalities might themselves play a role in triggering the illness (Nishita & al., 1986; Rechlin & al., 1998). Exploring the endocrine and autonomic disturbances associated with ED is essential in order to understand the symptomatology of eating disorders.

1.1.1 Autonomic system disturbances

Hypotension (low blood pressure) and bradycardia (abnormally slow heart beat) are typically observed in patients with eating disorders (Emmett, 1985; Pirke, 1996; Kennedy & al., 1989). Moreover, cardiovascular complications are the major cause of premature death in patients with AN. Most of these complications are thought to result from disturbances of the autonomic nervous system (ANS). More specifically, bulimia is associated with increased vagal activity (i.e. increased parasympathetic activity) coupled with reduced sympathetic activity (Kennedy & al., 1989; Nishita & al., 1986). In

[2] Homeostasis refers to the maintenance of the internal environment to a stable condition or equilibrium.

anorexics, decreases in both the parasympathetic and sympathetic activity have been observed, the decreased sympathetic tone being most prominent (Rechlin et al, 1998). Although the specific changes in parasympathetic and sympathetic activity are different for the bulimics and anorexics, they result in the same imbalance (increased parasympathetic/ sympathetic ratio) and thus are expressed similarly (i.e. bradycardia, hypotension).

Disturbances in thermoregulation[3] are also common in ED patients. For example, hypothermia, defined as a core temperature below 35-36.1 °C, is a frequent symptom of AN (Emmett, 1985; Hoek & al., 1998; National Asssociation of Anorexia Nervosa and Associated Disorders [ANAD]; Nishita & al., 1986). The majority of physiologic alterations associated with starvation return to normal after reffeeding, however, abnormalities in thermoregulation persist after recovery from AN suggesting hypothalamic abnormalities might have been present prior to the onset of the illness (Nishita & al., 1986; Rechlin & al., 1998).

Mechanisms involved in thermoregulations are tightly regulated by the autonomic nervous system. The reticular formation receives information about average skin temperature from large skin surfaces and conveys this information to neurons in the preoptic and anterior hypothalamus (PO/AH). The PO/AH also contains thermosensitive neurons that sense core temperature from the circulating blood around the hypothalamus. Neurons in the PO/AH are thought to be central to thermoregulation because 1) they are capable of integrating both central and peripheral thermal information and 2) they send axons throughout the nervous system to control a variety of autonomic and behavioural thermoregulatory responses (for review see Blatteis, 1998).

Because patients with AN suffer extreme losses of fat and lean muscles as a result of starvation causing the insulation of their body core to decrease dramatically, their autonomic and endocrine systems are forced to undergo massive adaptations in order to restrict energy expenditure and protect the body from experiencing fatal hypothermia. These adaptations are reflected by acrocyanosis, marked peripheral vasoconstriction, absence of normal diurnal temperature cycle, frequent complains about “feeling cold”,

[3] Thermoregulation refers to the capacity of mammals to maintain their body temperature within a narrow range of temperature.

abnormal sweating following a meal, absence of shivering and many more. (for review of thermoregulatory abnormalities associated with AN, see Nishita & al., 1986) .

1.1.2 Endocrine system disturbances.

Alterations in the endocrine system following AN, BN or starvation have been widely documented by the research and clinical communities (Brambilla & al.,1985; Emmett, 1985; Koo-Loeb & al., 1999; Kaye & al., 1998; Pirke & al., 1985; 1996). Amenorrhea, a mandatory criterion for AN diagnosis according to the DSM-IV, is the most common physical manifestation of the alterations the endocrine system undergoes following the onset of AN. Amenorrhea is thought to be a consequence of reduced oestrogen levels due to a reduced production and secretion of gonadotrophins (LH and FSH). This is substantiated by the decreased LH response to gonadotrophin-releasing hormone (GNRH) characteristic of patients with AN (Emmet, 1985). In addition, the endocrine system regulates a variety of vegetative functions, mostly through the autonomic system, that are often altered prior to the development of full-blown illness in patients with eating disorders. These include: metabolic regulation, thermoregulation, cardiovascular function, hunger and satiety.

1.2 Pain

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (IASP). Congenital insensitivity to pain, a genetic disorder of autonomic system development, demonstrates the importance and value of pain. Patients with congenital analgesia suffer extensive injuries to joints as well as burns and lacerations that result in premature death. (Adams, 2003) Moreover, congenital analgesia is associated with abnormalities in other critical functions such as sucking, thermoregulation and gut motility, which implies that pain is mediated by the ‘primitive’ portion of the nervous system. (Adams, 2003; McMahon & Koltzenburg, 2006)

Pain can be either acute or chronic. Acute pain is short lasting; it is associated with tissue damage, and it resolves once the damaged tissue has been repaired. Acute pain arises from the stimulation of pain receptors and constitutes a normal response to injury. (McMahon & Koltzenburg, 2006; Rice & al., 2003). On the other hand, chronic pain is abnormal; it is enduring and it often arises and/or persists in the absence of any observable injury. Chronic pain can be due to persisting tissue pathology as in arthritis or be consequent to injury to nerves at some level of the nervous system (McCorry, 2004; Rice & al., 2003) Not only does chronic pain not seem to serve any useful purpose, but it is also highly detrimental to a person's health and well-being, making it a serious health problem. (McMahon & Koltzenburg, 2006; Rice & al., 2003)

Pain sensitivity can be described in terms of threshold or tolerance. Pain threshold refers to the point at which a physical stimulus becomes painful, while pain tolerance refers to the intensity of a painful stimulus a person will accept. (Fillingim, 2005) Since pain thresholds are closely related to a level of stimulation that would cause tissue damage it is not surprising that they are generally similar for everyone (Beecher, 1957). In contrast, pain tolerance can be highly variable with situation and culture (Fillingim, 2005).

Pain can also be classified in terms of nociceptors[4] and/or tissues it originates from: cutaneous, somatic or visceral pain (Kazanowski & Laccetti; 2004). Cutaneous pain refers to pain that arises from the skin or superficial tissues. Cutaneous nociceptors are situated just below the skin, and produce a well-defined, localized pain of short duration. (Rice & al., 2003; Wolff & Jarvick, 1964)

Somatic pain refers to pain in the muscles, ligaments or bones. (Rice & al., 2003) Somatic pain is usually more dull, less localized and of longer duration than cutaneous pain. (Kazanowski & Laccetti; 2004) Although both bone pain and muscle pain are classified as somatic pain, their specific quality and intensity are distinct; pain originating from the bones ususally being significantly more dull and intense than pain originating from the muscle. (Kazanowski & Laccetti; 2004) Visceral pain arises from the viscera or internal organs (Ness & Gebhart; 1990). Visceral pain is usually associated with

[4] Sensory receptors specific to pain stimuli

autonomic changes (eg. sweating) and is poorly localised and aching. (Kazanowski & Laccetti, 2004; Ness & Gebhart ; 1990))

A variety of methods exist to induce and measure acute pain experimentally in humans. (Beecher, 1957) Some of the most commonly used are: heat pain, cold pain, pressure pain[5] and ischemic pain. (O'Driscoll & Jayson; 1982)

Heat and cold pain can be induced experimentally using two different methods: the immersion of a hand in hot/cold water or the application of a small heated/cooled thermode on the skin (O'Driscoll & Jayson; 1982). In the first method, the painful stimulus (heat or cold) is applied to the whole hand and it is an indicator of thermal nociception in the vasculature, deep somatic tissue as well as cutaneous tissue. On the other hand, when one uses the thermal electrode, the painful stimulus (heat or cold) is applied to the skin only and thus, is an indicator of cutaneous somatic pain only. [6]

Pressure pain is usually induced by applying pressure to specific muscles regions (tender areas) or by applying pressure to specific articulations (bones, ligaments and muscles). Since the painful stimulus (pressure) is applied on musculoskeletal tissues (i.e. muscles, ligaments or bones), pressure pain is an indicator of deep somatic pain. (Skyba & al., 2005)

One should not assume that the application of pressure to the hands versus the application of pressure to muscle tender areas on other parts of the body are interchangeable. In fact, by applying pressure on the hands specifically, one measures pain primarily on ligaments and bone structures, while by applying pressure on muscle tender areas, one measures pressure pain on muscle tissue predominantly. (McCorry, 2004)

Ischemic pain is usually induced by installing a tourniquet on the upper arm and asking the participant to perform handgrip exercises (Maurset & al., 1991). This causes ischemia after a short period. Ischemic pain is an indicator of deep somatic pain. Ischemic pain is thought to be mediated by ASIC 3 receptors mainly because ASIC3 receptors have the ability to detect small decreases in ph when low oxygen levels are present, the hallmark of ischemia (Naves & McCleskey, 2005). In contrast, pressure pain,

[5] Also referred to as mechanical pain
[6] See Wolff & Jarvick (1964) for a discussion on superficial and deep somatic tissue thresholds

a measure of deep somatic pain as well, is mediated by mechanical nociceptors, sensory receptors that react to high amount of pressure. (McCorry, 2004)

As the pain system is one of the most important and 'primitive' systems of an organism, by exploring the relationship between eating disorders and pain sensitivity, we will be able to enhance the scientific community's understanding of the pathophysiology of eating disorders, as well as the neuropsychobiological systems that are involved in pain signalling and that are regulated by, amongst others, autonomic and endocrine action.

1.3 Pain thresholds in patients with ED

Table 1 summarizes previous studies that have assessed pain sensitivity and/or somatosensory function in ED patients. Elevated heat pain thresholds (de Zwaan, 1996; Lautenbacher, 1990; Lautenbacher, 1991a, Papezova, 2005; Pauls et al., 1991); elevated pressure pain thresholds (de Zwaan 1996; Faris, 1992;1998 and Raymond 1991a) and elevated ischemic pain thresholds (Girdler & al., 1998 and Stein & al., 2003) have been reported in patients with ED.

A variety of theories have been developed to explain the increased pain thresholds in patient with eating disorders but none have been substantiated. One of the attractive hypotheses previously proposed was that the elevated pain thresholds would be due to a hyperactive opioid system. However, Lautenbacher et al. (1990) demonstrated that the administration of naloxone did not normalize the elevated pain thresholds observed in both bulimics and anorexics.

Another interesting hypothesis that was suggested was that a polyneuropathy due to severe malnutrition was responsible for the increased pain thresholds in the anorexics (Lautenbacher & al., 1990). This hypothesis could not be substantiated either, since an examination of vibration, cold and warmth[7] thresholds in anorexics suggested no major somatosensory dysfunctions (Pauls & al., 1991). Nevertheless, the small sample size used in the study by Pauls et al. (1991) is a major issue. They only tested 9 patients in both the AN and BN conditions so it is not surprising that no statistically significant disturbances

[7] Cold and warmth thresholds refers to the moment at which the first sensation of cold or warmth is felt, not pain.

in sensory functions were observed. Interestingly, Pauls et al. (1991) noticed a small trend towards elevated cold and warmth thresholds in ED patients. They did not, however, interpret this trend as an indicator of somatosensory disturbances partly because the vibration thresholds seemed to be normal.

Sensory function has been evaluated to a greater extent in the case of BN, but the data are inconsistent. Specifically, Florin et al. (1988) found that bulimics exhibited elevated tactile thresholds (ability to detect innocuous stimulation of the skin) while Raymond et al. (1999a) and Faris et al. (1992) found the tactile thresholds to be normal for both AN and BN patients.

The study by Raymond et al. (1999a) is worth examining in more depth: not only is it the sole study that assessed pain tolerance in addition to pain threshold in patients with AN, but the authors also assessed tactile thresholds[8], as mentioned above. The study is not, however, free of concerns. First, Raymond et al. (1999a) used a simple ascending-descending method of limits test for tactile thresholds, a method yielding a 50% criterion level, that is chance level. We propose to examine how tactile sensitivity relates to pain sensitivity in patients with eating disorders by measuring tactile thresholds using a 2-down 1-up staircase method; a method which yield a 71% criterion level (see method section). A second concern with the study by Raymond et al. (1999a) is the sole use of a Ugo Basile Analgesiometer to measure pressure pain thresholds[9]. The tip of the device, which applies gradually increasing amounts of pressure, was positioned in the center of the participant's fingerprint on each of the four fingers of the nondominant hand in succession. Although the Ugo Basile Analgesiometer shows high accuracy and good test-retest reliability (Zwaan & al., 1996), it has been used primarily in pain studies with rats and little is known on its applications for human pain studies. Although this is not a huge concern per se, the fact that the other 4 studies that measured pressure pain thresholds in patients with EDs (de Zwaan & al., 1996; Faris, 1992; 1998 and Raymond, 1999b) also used a Ugo Basile Analgesiometer and moreover measured thresholds at the same location that Raymond et al. (1999) did, stresses the need for future research to assess pressure pain thresholds using different methods and on different body areas. Also, as

[8] ability to detect innocuous stimulation of the skin
[9] also referred to as mechanical pain threshold

mentioned in the discussion on pain measures, although the Ugo Basile Analgesiometer is often referred to as a measure of pressure pain because it literally applies pressure on the hands, it should not be mistaken with other measures of pressure pain such as measuring pressure pain on muscle tender areas all over the body (see discussion on pain measures).

We measured deep somatic pain across all four quadrants of the body and using two different methods: We used 1) an electronic Somatic Pressure Algometer to apply pressure at different locations on the body, a method which is routinely utilized in studies of fibromyalgia (Chaitow, 2002) and 2) a Ugo Basile Analgesiometer to apply pressure on the fingertips. It is, to our knowledge, the first attempt to measure pressure pain thresholds in ED patients across all four quadrants of the body. Moreover, by measuring pressure pain thresholds using two different methods, we wished to assess whether future researches should use multiple methods when measuring pressure pain in ED patients.

A noteworthy finding in the study by Raymond et al. (1999b) and Stein et al. (2002) was that pain tolerance in patients with eating disorders, once the differences in pain thresholds were accounted for, did not differ from normal individuals. The lack of disturbances in pain tolerance in patients with eating disorders has important theorical implications since it makes it unlikely that cognitive variables (e.g. need for control and perfectionism) or an hyperactive opiods system could be responsible for the elevated pain thresholds. Opioids and cognitive variables are both known to have a stronger influence on pain tolerance than pain thresholds. Additional assessments of pain tolerance are needed in order to substantiate the finding of Raymond et al.(1999b) and Stein et al. (2002). In other words, if future research demonstrates that pain tolerance is indeed normal in ED patients, as Raymond et al.(1999b) and Stein et al. (2003) have suggested, it would imply that cognitive factors or an hyperactive opiods system are both unlikely to be responsible for the disturbances in pain sensitivity in ED patients. In the present study, the relation between pain tolerance and pain thresholds in patients with eating disorders was examined by measuring and comparing pain tolerance to the ischemic pain test (see method section) to pain thresholds on the same test (ischemic pain test).

Table 1. Description of previous studies on pain in Eating Disorder patients.

The ED subtype, the stimuli used, the type of pain induced and the main results are described. Comments are also included if relevant.

Legend

Painful Stimuli:
PPT : Pressure Pain Threshold
HPT: Heat Pain Threshold
Threshold
IPT: Ischemic Pain Threshold

Non-nociceptive stimuli
VT : Vibration Threshold
PTT: Punctate Tactile

(Sensitivity to light touch)

Study	**Participants (ED subtype)**	**Stimuli**	**Results**	**Comments**
De Zwaan et al., 1996a; 1996b Note: the same data was used in both articles	- AN (n=22) - BN (n=18) - Controls (n=32)	- Heat pain (thermode) - Pressure pain (hand)	- BN: Elevated HT* and PPT* - AN: Elevated HPT* and PPT	- Alexithymia not correlated - Depression score modulates PPT* but not HPT
Faris et al., 1992	- BN (n=27) - Controls (n=32)	- Pressure pain (hand) - Tactile perception (sensitivity to light touch)	- Elevated PPT* and tolerance* - Normal PTT	Tactile sensitivity was only tested on the fingers
Faris et al., 1998	- BN (n=14) - No Controls	Pressure pain (hand)	PPT* more elevated during inter-binge interval than following a binging/purging episode	Ondansetron normalized the observed effect of inter-binge interval (n =11)
Florin et al, 1988	- BN (n=14)	Tactile perception (sensitivity to light touch)	PTT* elevated	Tactile sensitivity tested on abdomen and hands
Girdler et al., 1998	- BN (n=14) - Controls (n=14)	Ischemic Pain	Elevated IPT* and tolerance*	IPT correlated with systolic BP in the bulimics

Study	Participants (ED subtype)	Stimuli	Results	Comments
Krieg et al., 1993	- AN (23) - Restrained eater (21) - Unrestrained eater (20)	Heat Pain (thermode)	HPT normal for all groups	Negative correlation between skin T° and HPT in the "poorest outcome" AN group
Lautenbacher et al., 1990	- AN (n=10) - BN (n=10) - Controls (n=11)	- Heat Pain (thermode)	- BN: Elevated HPT* - AN: Elevated HPT in some	- Naloxone had no effect on HPT - Plasma Cortisol not correlated
Lautenbacher et al., 1991a	- AN (n=19) - BN (n=20) - Controls (n=21)	- Heat Pain (thermode)	- BN: Elevated HPT* - AN: Elevated	Negative correlation between skin T° and HPT in AN group
Lautenbacher et al.,1991b	Healthy women following a 3 week 1000kcal diet (n=11)	- Heat pain (thermode) - Warmth and Cold perception - Vibration	No changes in any of the sensory measures following the diet	
Papezova et al., 2001	- AN (n=8) - BN (n= 6) - No controls	- Heat pain (thermode)	Elevated HPT in AN Normal HPT in BN	Parabolic relation of melatonin with HPT, median levels being associated with the lowest HPT
Papezova et al., 2005	- AN (n=21) - BN (n= 18) - Controls (n=17)	- Heat pain (thermode)	Elevated HPT*	HPT* elevated to a greater extent in the binge/purging anorexics and bulimics

Study	Participants (ED subtype)	Stimuli	Results	Comments
Pauls et al., 1991	- AN (n=9) - BN (n=10) - Controls (n=10)	- Heat pain (thermode) - Warmth and Cold perception - Vibration	- Elevated HPT* - Trend towards elevated warmth and cold perception thresholds -Vibration normal	Small sample makes interpretation difficult
Raymond et al., 1999a	- AN (n=43) - Controls (n=65)	- Pressure pain (hand) - Tactile perception (sensitivity to light touch)	- Elevated PPT* and tolerance* - Normal PTT	Once differences in pain thresholds are accounted for, the tolerance is normal
Raymond et al., 1999b	- BN (n=9) - No Controls	- Pressure pain (hand)	- Post-vomit episode correlated with highest PPT	
Stein et al., 2003	- Recovered BN (n=11) - Controls (n=15)	- Heat pain (thermode) - Ischemic pain	- HPT: analyses impossible - Elevated IPT* and normal tolerance	Analyses of HPT was impossible due to a lack of useable data

1.4 Methodological Concern in ED studies

Although the majority of the data suggests ED patients have elevated pain thresholds, there is some controversy on the subject. One should be careful when interpreting the results of studies assessing pain threshold in ED patients because they, by in large, only measured cutaneous pain perception. For example, heat pain threshold, a measure of cutaneous pain perception, was used as the sole measure of pain threshold in the studies by Krieg & al. (1993); Lautenbacher & al. (1990) Lautenbacher & al.(1991a); Lautenbacher & al. (1991b) ; Papezova & al.(2001); Papezova & al. (2005) and Pauls & al., (1991). De Zwaan & al. (1996b) concludes, after comparing pressure pain thresholds to heat pain thresholds, that the "minimum correlation of 0.5 (that) would justify allowing one test to be considered equivalent to another is not met."

Only 5 studies measured pressure pain thresholds, a measure of deep somatic pain, in ED patients. (de Zwaan & al., 1996; Faris & al., 1992; Faris & al., 1998 and Raymond & al., 1999a, 1999b, see Table1). Of these 5 studies, the location of stimulation is always on the hands and it is not indicated whether soft tissue (i.e. ventral) or bones and ligaments (dorsal) were tested. Besides, two of these studies (Faris & al., 1998 and Raymond & al., 1999b) did not have any normal participants (i.e. controls).

No study has ever assessed ischemic pain thresholds in anorexics, and only the studies by Stein et al. (2003) and Girdler et al. (1998) have measured ischemic pain thresholds in bulimics.

What is more, no study has ever examined pain sensitivity (1) all over the body, (2) using at least three methods that are known to elicit different forms of pain (i.e. cutaneous pain vs deep somatic pain vs ischemic pain) and (3) have also tried to assess tactile sensitivity[10]. This lack is of tremendous importance since our current understanding of many pain-related disorders suggests that an examination of pain sensitivity all over the body and using different methods is essential when one tries to explain disorders characterized by disturbances in pain perception. Most pain-related syndromes, such as fibromyalgia and other functional pain syndromes can, indeed, only

[10] Sensitivity to light touch

be understood in terms of a generalised disturbance in sensory function and nociception. The rational that a general evaluation of sensory function is required in order to understand specific disturbances in nociception, is further supported by (1) clinical data suggesting that patients with fibromyalgia[11] exhibit a generalized deep muscle pain across all four quadrants rather than a specific, localised pattern of pain and (2) that depressed individuals typically complain of multiple aches and pains rather than pain at any particular location (Dworkin & al., 1990).

We are the first study to measure 1) punctate tactile thresholds[12] in ED patients at 3 different locations (i.e. bilaterally at forearm, knee, trapezius; see methods) and 2) pain sensitivity all over the body, using 3 different methods (i.e., pressure pain over the body, pressure pain on the hands and ischemic pain; see methods).

1.5 Pain, depression and anxiety disorders in patients with EDs

Although AN and BN are disorders in their own right, they are very frequently accompanied with depression (Emmett, 1985; Eckert, 1982; Koo-Loeb, 2000; Lucka, 2004) and/or anxiety (Emmett, 1985; Godart & al., 2003; Holtkamp & al., 2005; Koo-Loeb, 2000). Braun (1994) found that depression, anxiety and substance abuse were the most common comorbid diagnoses. Moreover, Kaye et al. (2004) reported that the onset of anxiety disorders often preceded the onset of an eating disorder, suggesting a possible underlying vulnerably to both disorders. The comorbidity of anxiety and/or depression with eating disorders is of special interest in this study because alterations in pain sensitivity have not only been reported in patients with eating disorders, but also in patients with major depression (Adler & Gattaz, 1993; Hall and Stride, 1954; Meagher & al. 2001; Merskey 1965; Pinerua-Shuhaibar & al. 1999; Weisenberg & al., 1998; Zelman, Howland & al. 1991;) and in patients with anxiety disorders. (Keogh & Birkby, 1999; Kopp & Gruzelier, 1989; Nishith, Griffin & Poth, 2002). Findings from studies assessing pain sensitivity in patients with anxiety or depressive disorders are, however, somewhat ambiguous. For example, Keogh and Birkby (1999) found that females who were higher

[11] Fibromyalgia is a chronic syndrome characterized by diffuse pain, and fatigue.
[12] Sensitivity to light touch

in anxiety sensitivity reported higher level of sensory pain while, somewhat paradoxically, Nishith et al. (2002) found evidence for what he called "stress-induced analgesia" in battered women with post-traumatic stress disorder. Similar ambiguities can be found in depression studies: studies using a sustained noxious stimulus have generally reported a lower pain tolerance in patients with MDD (Merskey 1965; Pinerua-Shuhaibar et al. 1999) and healthy subjects with experimentally induced depressed mood (Zelman & al. 1991; Weisenberg & al., 1998 and Meagher et al. 2001) while studies that have used thermal or electrical stimulation have usually found elevated pain thresholds in depressed individuals (Adler and Gattaz, 1993; Hall and Stride, 1954)

In the present study, we investigated how the incidence of concurrent depressive and/or anxious symptoms in patients with eating disorders might relate to sensory and autonomic functions with the aim of increasing the scientific community's understanding of the relation between depression, anxiety, eating disorders and autonomic and sensory functions.

1.6 Pain and Autonomic disturbances in patients with EDs

Pain and the autonomic nervous system are closely integrated in CNS regions that are critical for adaptation and survival in response to internal and external challenges – ie, stress. In these regions, neurons often respond to both nociceptive and viscero-sensory information and act to initiate autonomic and behavioural responses to noxious stimuli. Sympathetic outflow can also modulate pain sensitivity in the periphery. For example, sympathetically maintained pain (SMP) is a chronic pain syndrome in which light mechanical and thermal stimuli evoke pain (Baron et al. 1999; Janig and Baron 2002; Janig 2003), and it can be relieved by blockade of sympathetic outflow to the affected region (Baron et al. 2002). Understanding the ANS disturbances associated with EDs might, therefore, be key in understanding the elevated pain thresholds. In this study, we explored autonomic function using basal blood pressure and a non-invasive method by which the resting tone and reactivity of the sympathetic and parasympathetic systems can be estimated, analysis of heart rate variability (HRV).

The vagus nerve is critical in peripheral control of satiety, heart and other visceral functions, as well as modulating nociceptive function directly and indirectly (Faris & al., 1992; Stein & al, 2003). In view of that and the fact that hypervagal activity is frequently reported in women suffering from BN (Kennedy & al.,1989; Rissanen & al., 1998), some theorists have suggested that the abnormalities in vagal function may underlie both the elevated pain threshold and the abnormalities in the satiety response observed in bulimia nervosa (Faris & al., 1998; Raymond & al, 1999b). Studies that have tried to assess the possible involvement of the vagus nerve in BN hypoalgesia have, however, yielded mixed results. For example, Faris et al (1998) measured the effect of ondansetron, a 5-HT3 receptor antagonist known to decrease vagal tone, on pressure pain thresholds in patient with BN and found that ondansetron not only normalized the pain thresholds but also reduced the frequency of the binge-eating/purging episodes. In accordance with this finding, in a study by Papezova et al. (2005), individuals with binge-purging symptomatology exhibited the highest pain thresholds. Conflicting with these results is the study by Raymond et al. (1999a). They hypothesized that the abnormalities in vagal tone of BN patients and AN patients were responsible for the elevated pain threshold. They could not, however, show any correlation between the number and frequency of binge-eating/vomiting episodes and pain threshold, leading them to decide that the involvement of the vagus nerve was improbable. Although the specific involvement of the vagus nerve in the elevation of pain threshold is highly debatable, it underlines the interrelatedness between the autonomic system and the control of vegetative and nociceptive functions.

In light of the facts discussed above, a promising explanation for the increased pain thresholds observed in patients with eating disorders would be that the alterations in the autonomic nervous system in AN and BN influence pain sensitivity. Nevertheless, it should be emphasized here that although disturbances in the autonomic system might explain the elevated pain thresholds in both AN and BN patients, it is likely that the specific mechanisms through which the autonomic disturbances affect pain sensitivity are different for AN and BN. That is, the specific mechanism responsible for the hypoalgesia in women suffering from AN might not be the same as the one responsible for the hypoalgesia in women suffering from BN, although both could relate to disturbances in

autonomic functions. For example, BN patients could show elevated pain threshold because of repeated vagal afferent activation while AN patients could show elevated pain threshold because of decreased sympathetic activity. Most theorists seem, indeed, to agree that the elevated pain thresholds observed in BN and AN both reflect abnormalities in autonomic functions but that the specific mechanism through which the autonomic disturbances affect pain sensitivity are different for AN and BN. This is coherent with previous studies that have suggested a negative correlation between pain threshold and skin T° in women suffering from AN (Krieg & al, 1993; Lautenbacher & al., 1991a; Papezova & al., 2004) while suggesting a correlation between pain thresholds and binge/purging behaviours and/or body weight in bulimics (Faris & al., 1992, 1998; Papezova & al., 2005; Raymond, 1999b). By measuring HR, BP and HRV, we were able to further investigate the relation between autonomic function and pain sensitivity in patients with eating disorders. Additionally, we tested the hypothesis that anorexic and bulimic symptomatologies might be related to different contributions to the elevated pain thresholds by comparing pain thresholds on the basis of the magnitude and frequency of restrictive and/or binge-eating/purging behaviours.

Sensitivity to experimental pain is not independent of resting blood pressure: higher blood pressure being associated with lower pain sensitivity. (al'Absi & al., 2002; Bruehl & al., 2002; Edwards & Fillingim, 2001). The majority of AN patients show hypotension (decreased blood pressure) but, as mentioned earlier, most AN patients also show increased pain thresholds, an association somewhat paradoxical to the above mentioned relationship between blood pressure and experimental pain.

The relationship between blood pressure and BN seems to be rather different from the one between AN and blood pressure as the majority of patients with BN show normal blood pressure, as opposed to the characteristic hypotension exhibited by AN patients. Of special relevance here is the study by Girdler et al (1998) since they found a positive correlation between pain threshold and systolic blood pressure during the testing of ischemic pain. This, in turn, motivated the author to suggest BP-related hypoalgesia as a good candidate for explaining the elevated pain thresholds in women with BN. BP-related analgesia in BN seems, however, improbable since Girdler and its co-workers could not

explain the fact that there was no difference between the BP of women suffering from BN and the BP of normal individuals.

In the present study, we investigated the relation between blood pressure, experimental pain and eating disorders by measuring blood pressure at rest and following an orthostatic challenge (see method section for detailed description) This examines regulation of BP as opposed to simply looking at resting level.

Orthostatic hypotension is defined by The American Autonomic Society (AAS) and the American Academy of Neurology (AAN) as a systolic blood pressure decrease of at least 20 mm Hg or a diastolic blood pressure decrease of at least 10 mm Hg within three minutes of standing up. When an adult rises to the standing position from a supine position, 300 to 800 mL of blood accumulates in the lower extremities. In order to maintain blood pressure while changing from a horizontal to a vertical position, many finely-tuned cardiovascular, and autonomic responses must take place rapidly. When a person stands up, the resulting drop in blood pressure drives a coordinated increase in sympathetic outflow, such that arteries are constricted to increase blood pressure and reduce the tendency for blood to accumulate in the lower extremities, and heart rate is increased (for review, see Bradley & Davis, 2003). Impairment of the sympathetic nervous system is therefore likely to result in orthostatic hypotension or a least a "less than normal" increase in blood pressure following standing up. We took advantage of the link between sympathetic disturbances and orthostatic hypotension by collecting measures of blood pressure and heart rate following an orthostatic challenge (see method section for detailed description) using this measure as an indicator of autonomic abnormalities.

Both the sympathetic nervous system and the parasympathetic nervous system control the heart. These two systems are mainly opposed to each other and the "tension" between them is reflected, in the heart, by small variations in the beat to beat interval referred to as heart rate variability (HRV). Impairment in one of these systems often results in a reduction of this variability due to the domination of one system over the other. Using spectral analysis of the heart rate, these slight variations can be quantified and divided into the high frequency power (HF) component of the HRV spectrum (0.15 to 0.40 Hz), a relatively pure measure of cardiac parasympathetic activity (Eckberg & al.,

1980) and the low-frequency power (LF) component of the HRV spectrum (< 0.15 Hz), a measure of both sympathetic and parasympathetic activity (Malik & Camm, 1993). Accordingly, the LF/HF ratio is thought to be an index of sympathovagal balance (Lombardi & al., 1987).Stress is associated with an increase in sympathetic cardiac control and/or a decrease in parasympathetic control, increasing LF power, decreasing HF power, and/or increase in the LF/HF ratio. This general response pattern holds for acute psychological stressors such as mental arithmetic and reaction time tasks (Berntson & al., 1994; Delaney and Brodie 2000; Friedman & al., 1996; Hughes & Stoney 2000; Jain & al., 2001), and for real-life acute stressors such as college examinations, earthquakes, and typical day-to-day hassles (Sloan & al., 1994).

Recent studies demonstrated a reduced HRV, particularly in the low frequency spectrum, in patients with AN (Melanson & al., 2004; Nishita & al., 1986 and Rechlin & al., 1998). This finding is consistent with previous findings of altered sympathetic control of the heart in patients with AN. (Casu & al., 2002 and Galetta & al., 2003) The reduced sympathetic activity observed in patients with AN is of particular interest in this study since Krieg & al. (1993) and Lautenbacher & al. (1991) both found a correlation between skin temperature and pain thresholds; two measures known to be influenced by sympathetic activity. Sympathetic functions might be, indeed, the missing link influencing both pain sensitivity and skin temperature in anorexics.

As well, recent studies have demonstrated a reduced sympathetic activity accompanied with an elevated cardiac vagal tone and reduced heart rate in patients with BN.(Kennedy 1989; Rissanen, 1998). The hypervagal activity observed in patients with BN is noteworthy as Faris et al. (1998) and Raymond et al. (1999b) found a correlation between the frequency of binge/purging episodes, a behaviour that would activate the vagus nerve, and pain thresholds in patients with BN.

By means of combining measures of blood pressures (while resting and following an orthostatic challenge) and HRV we were able to investigate the relationship between autonomic abnormalities and pain sensitivity in patients with EDs.

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1.7 Skin Reactivity in patients with eating disorders

In addition to relaying information to drive protective reflexes, one class of neurons involved in pain also produces a component of the inflammatory response, the axon reflex. The axon reflex can be easily assessed by applying capsaicin to the skin, and measuring the size of the flare that is produced. The axon reflex reflects the fact that the unmyelinated fibres innervating the skin branch out into a tree of terminals. When one part of the tree of any given neuron is activated by intense stimulation, the axon potential spreads into the tree as well as being conducted to the spinal cord. Substance P is then released in the terminal branches causing vasodilation, which is observed as reddening of the skin as blood flow increases in order to deal with a threat to tissue. Capsaicin is the active ingredient in chili peppers, and its hot, burning property is produced specifically by release of substance P (McMahon & al., 1997). The size of the flare is proportional to the quantity of substance P released. In at least one condition, generalized hypersensitivity to pain is thought to be due to increased response of these primary afferents to produce persisting amplification of nociceptive afferent input. Thus, (Littlejohn & al., 1997), reported increased flare on application of capsaicin in patients with fibromyalgia, a functional pain syndrome. More recently we have found that young women, normal except for low mood, have decreased response to capsaicin, and this was correlated with decreased tactile sensitivity (Lehoux et al, in preparation). We believe that our finding reflects an effect of chronic stress and are currently further investigating the finding.

In this study, we measured skin reactivity, in particular its inflammatory response to capsaicin (see method), to assess if pain sensitivity and tactile sensitivity are related to skin reactivity in ED patients.

1.8 Medical complications in patients with eating disorders

A number of medical illnesses co-occur with AN and BN. Some of these illnesses are quite painful such as gastroduodenal ulcers, upper abdominal pain, constipation, fibromyalgia and migraines. It is surprising that none of the studies assessing pain perception in patients with eating disorders recorded information about the occurrence of

painful illnesses in their patient groups, particularly in light of the symmetrical and strong relationship between pain and psychological disorder (Gureje & al., 2000). That is, pain predicted the later onset of a psychological disorder; and psychological disorder predicted the onset of persistent pain. Interestingly, the common occurrence of painful illnesses in ED patients and the reports of elevated pain threshold in ED patients could both reflect general disturbances of the pain system. We investigated concurrent painful conditions in patients with eating disorders with the aim of evaluating their possible contribution to pain perception.

1.9 Proposed Study

In view of the facts discussed above, we hypothesized that there are abnormalities in pain sensitivity in patients with eating disorders that are related to disturbances in the autonomic system. In the case of women suffering from AN, we expect increased pain thresholds to be associated with a reduced heart rate variability due to a decreased sympathetic drive, abnormal (i.e. decreased or increased) secretion of substance P and importantly, a decreased sympathetic response to a stressor. In the case of women suffering from BN, we expected increased pain thresholds to be associated with a higher frequency and severity of binge-eating/purging behaviors, abnormal secretion of substance P, reduced heart rate variability due an overactive parasympathetic system, and a relatively normal sympathetic response to a stressor. Possible covariates such as extreme exercise or the concurrence of highly painful medical illnesses (e.g. gastrointestinal disorders) were also explored.

The measures of sensory function that were used were chosen because they are reliably different and minimally invasive. Combined, they yielded a broad assessment of somatosensory function in patients with eating disorders. They included tactile thresholds for punctate stimuli; pressure pain thresholds on the non-dominant hand and over tender points that are included in the definition of fibromyalgia; ischemic pain threshold and tolerance; and a set of questionnaire listing common types of somatic pain. We also used a set of questionnaires to evaluate eating disorder symptomatology, general mental and physical health, depression and anxiety and other psychopathologies, possible contributors such as severity of the malnutrition and the co-ocurrence of painful medical

complications. In addition, heart rate variability and blood pressure were assessed, since autonomic function could be the link influencing pain sensitivity, peripheral thermoregulation and binge-eating/purging episodes in patients with eating disorders.

The primary goal of the present study is to better describe the relationship between eating disorders and psychological, autonomic and somatosensory functions, in particular pain thresholds and tolerance, in a way that enhances our knowledge of the pathophysiology of eating disorders.

By studying pain and sensory perception in ED patients, we hope to provide new insights into the pathophysiology of eating disorders. The description of psychiatric syndromes in terms of neurobiological abnormalities, including abnormalities of pain perception, may also be a useful addition to the conventional classification, which only relies on psychopathological features. Finally, data could suggest new approaches to treatment of EDs

CHAPTER 2

MATERIAL AND METHODS

2.1 Participants

23 females suffering from an ED (in and outpatients) and 16 demographically-matched (race, age, education) controls were recruited as participants. Participants constituting the AN groups (i.e. AN Binge/Purge Subtype and AN Restrictive Subtype) where recruited if they had a diagnosis of AN according to the DSM-IV prior to starting treatment. Further classifications into subtypes are discussed in the results section. BN patients where recruited if they had a diagnosis of AN according to the DSM-IV prior to starting treatment. The decision to recruit both inpatients and outpatients was taken 1) to increase our "pool" of suitable participants and 2) to ensure that we recruit a representative sample of the overall ED population because inpatients and outpatients, although similar in many regards, tend to differ in their medication intake as well as their level of emaciation. We restricted the sample to females because 1) the prevalence of AN and BN in females is tenfold that of men and 2) it removes a possible source of variability. Since medication (mostly psychoactive) is commonly prescribed to ED patients , medication did not constitute an exclusion criterion. Instead, statistical analyses were carried out to determine whether patients using medication differ from medication-free patients.

All ED patients were in treatment at the time of testing. Treatments varied substantially from patients to patients, ranging from low intensity outpatient to partial and full hospitalization. Since EDs patients regularly suffer relapses and do not necessarily "accept or participate" to their treatment, it was not possible to evaluate meaningfully the time they had been in treatment before testing. Instead, the age at which they received their first diagnosis of an ED was recorded and showed that patients had been diagnosed for periods ranging from 1 year to 25 years before being tested. Most of the diagnoses were made by general practitioners and patients were generally referred to specialized eating disorder clinics a few weeks or months later. While in treatment, 3 AN patients,

although still very thin, had reached a normal weight BMI (≥ 18) at the time of testing. Also, 1 BN patient did not have any binge/purge episodes for 3 months or more prior to the time of testing.

Both outpatients and inpatients were recruited at the Specialized Eating Disorder Program of the Douglas Hospital. After giving written or verbal consent to be approached by an experimenter, volunteers were introduced to the study and screened for suitability either in person or by telephone. If agreeable, they were then contacted a second time to arrange an appointment for testing.

For the control group, 5 participants were recruited through the "snow-ball" method. The "snow-ball" method consists of recruiting controls through the help of the patient groups. That is, at the end of the testing session, participants from the patient groups were asked if they know a friend who doesn't suffer from an eating disorder and who might be interested in participating in the study. The participant was then asked to contact the friend in question and ask them if they would consent to the experimenter calling to introduce the study. After consent was obtained, the experimenter phoned the friend in question, introduced the study, screened for suitability and scheduled a time for testing if they were agreeable.

The "snow-ball" method was selected because it an effective approach to recruiting demographically matched controls. Since controls recruited through the snow-ball method are within the immediate social sphere of the participants in the patient groups, they tend to share the same demographic characteristics and tend to have similar environments and activities. The 11 remaining controls were recruited through advertisements placed on the bulletin boards across McGill campus. Volunteers were reached, screened for suitability and introduced to the study either by telephone or by email by one of the experimenter. When agreeable, participants were reached a second time to arrange a time for testing.

In addition to the above-mentioned selection criteria specific to each group, all participants were selected according to the following inclusion and exclusion criteria:

Inclusion criteria:

1) informed consent to participate;

2) between 18 and 45 years of age and able to speak and read English or French;

3) no neurological disorders (by self-report)

Exclusion criteria:

1) surgery or significant physical injury within the past 3 months;

2) chronic dermatological conditions of any aetiology on any of the sites to be tested;

3) taken analgesic medication within 8 hours before testing;

4) Comorbid serious substance abuse problems as indicated in the hospital chart (patients only) or by self-report (controls only). Since many ED patients are heavy smokers, cigarettes addiction was not a criterion for exclusion. Also, since occasional use of marijuana is common amongst young women, and it is not an addiction, it did not serve as a criterion for exclusion.

Participants were compensated 20$ for their participation in the study. No participants drop out during the testing session.

2.2 Measures

2.2.1 Eating disorder symptomatology

The eating disorder symptomatology was measured using the Eating Disorder Examination Interview (EDE-I). The EDE-I was conducted by a trained assessor that is proficient in both English and French**.** The EDE-I is a standardized semi structured interview that quantify the symptoms, behaviours and cognitions that are typically associated with eating disorders such as daily dietary intake and body dissatisfaction. The EDE-I was selected because 1) it is the "gold standard" diagnostic tool for EDs (Fairburn & Beglin, 1994; Guest, 2000); 2) it is relatively fast and easy to administer (i.e. 20 minutes); and 3) it shows reliability, high validity and consistency (Beumont & al., 1995; Rizvi & al, 1999; Guest, 2000). Duration of the illness, body mass index and last known menses are also recorded in the EDE-I.

2.2.2 Demographic and lifestyle

General information about the participant's lifestyle and demographic characteristics was obtained using a set of questions regarding age, alcohol and drug intakes, medication use, level of activity, etc. A checklist of 19 commonly experienced pains was also included in this section. Using two 3 points-rating scales, the participants specified the frequency, and intensity at which the specific pains are experienced. The duration of the painful condition was also recorded.

2.2.3 Overall Health

Overall health was assessed using the Medical Outcome Study Short Form (SF-36). The SF-36 is a 36-items questionnaire where physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, mental health, vitality, bodily pain, and general health perception are evaluated. We selected the SF-36 because it is short, widely use, psychometrically sound (Ware & Sherbourne, 1992) and has shown validity and reliability in health surveys (McHorney & al., 1994).

2.2.4 Psychopathologies

The presence of comorbid psychopathologies was assessed using the Symptom Checklist 90 Revised (SCL-90-R). The SCL-90-R is 90-items scale that was designed in 1980s by Derogatis to screen for psychological disturbances in the normal, medical and psychiatric population (Croft, 1999) The participant is asked, using a five-point (0-4) ranging from "not at all" to "extremely" to rate the severity of somatic or psychological complaints. The SCL-90-R covers nine primary symptoms dimensions: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. Scores on these nine primary symptoms dimensions were calculated as a percentage of symptom severity (0-100); 0 % indicating the absence of symptom and 100% indicating the presence of all symptoms at maximum

intensity. In addition to scores on each of the nine symptoms dimension, the SCL-90-R also includes the Global Severity Index (GSI) and the Positive Symptom Distress Index (PSDI). The GSI measures overall psychological distress and is rated as the mean distress rating on all 90 items (0-100) while the PSDI measures the intensity of the symptoms and is rated as the mean distress of all 90 items not rated as zero (0-100). Besides being easy to administer and calculate, Croft (1999) concluded the SCL-90-R has high test-retest and internal consistency.

2.2.5 Anxiety and Depression

Although the SCL-90-R assesses anxiety and depression (along with other psychopathologies), the SCL-90-R is insufficient in view of the fact that anxiety and depression are the most prevalent comorbid psychiatric disorders observed in patients with ED. For that reason, an additional measure of anxiety and depression were collected using the Hospital Anxiety and Depression scale (HADS). The HADS was developed by Zigmond and Snaith (1983) to identify anxiety and depression among patients in non-psychiatric hospital clinics – i.e., those with physical illnesses. In the HADS, symptoms of anxiety or depression that frequently occur in physical illnesses, such as dizziness, headaches, insomnia, and fatigue, were excluded. Bjelland & al. (2002) published a review on the validity of the HADS based on almost 800 papers. He concluded that that HADS performs well in assessing the symptom severity and cases of anxiety disorders and depression in both somatic, psychiatric and primary care patients and in the general population. In addition to its wide use and its reliability, we selected the HADS because it is short and easy to analyze.

2.2.6 Pressure pain threshold (hand)

Pressure pain thresholds were assessed using a Ugo Basile Analgesiometer. The participants were instructed to place the distal-phalanx[13] of the fifth finger of their non dominant hand on a platform at the base of the instrument. The 1mm tip of a rubber cone

[13] Dorsal side, centered, on the first joint

was then lowered so that it was resting lightly on the finger. When the participant was ready, pressure was applied progressively by moving a weight along a worm gear by means of a small motor at a rate of 64g/s. Participant were instructed to pull out their finger, at the first sensation of pain. Removing the finger from the machine is easy and safe and it results in the immediate stopping of the motor. In order to prevent any injuries, the application of pressure was to be stopped before exceeding 1200g, an harmless amount of weight. (see deZwaan al, 1996a). After collecting mechanical pain threshold for the fifth finger, the same procedure was repeated for each of the four digits remaining (see Appendix 1). Mechanical thresholds were averaged across the five fingers. The use of the Ugo Basile Analgesiometer to induce pressure pain is safe and easy to administer. Moreover, it has been used previously to assess experimental pain in humans safely. (Faris et al., 1992; Faris et al., 1998; de Zwaan 1996a, 1996b; Raymond 1999a, 1999b)

2.2.7 Pressure pain threshold (across all four quadrants)

We measured pressure pain thresholds using an electronic Somatic Pressure Algometer (Jtech Digital Diagnostics). The instrument consists of a spring loaded stylus with a 0.5 cm diameter rounded rubber tip. It was applied manually, increasing the force by approximately one kilogram of pressure per second to the site to be tested, until the subject reported pain. The maximum pressure exerted by the device is 10 kg, which is not injurious. This method is used routinely in studies of fibromyalgia (Chaitow, 2002). Pressure pain thresholds were obtained over 8 body sites bilaterally location (see Figure). The sites tested are generally accepted as the tender points associated with fibromyalgia syndrome. More specifically, pressure pain thresholds were collected over the occiput (midline, at the suboccipital muscle insertions) low cervical area(bilateral, at the anterior aspects of the intertransverse spaces at C5-C7); trapezius (bilateral, at the midpoint ofthe upper border); supraspinatus (bilateral, at origins, above the scapula spine near the medial border); second rib (bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces); lateral epicondyle (bilateral, two centimetres distal to the epicondyles); gluteal (bilateral, in upper outer quadrants of buttocks in anterior fold of muscle); greater trochanter (bilateral, posterior to the trochanteric prominence); and the

knee (bilateral, at the medial fat pad proximal to the joint line). (See Appendix 2 for the specific location

2.2.8 Punctate Tactile Threshold

Punctate tactile thresholds were obtained using the Semmes-Weinstein Aesthesiometer Kit (Stoelting Co.). The standard fibres are constructed of 2" nylon filaments attached to 6" handles. The participant was asked to sit comfortably with eyes closed. The filament was placed on the skin, and pressure applied until the filament bended, with the bending strength of each filament dependent on its diameter. The filaments are smooth at the ends and cannot puncture normal skin. Thresholds for punctate tactile sensation were measured on sites that are all relatively hairless: trapezius (bilateral, at the midpoint of the upper border); volar surface of forearm (bilateral, centered); and the knee (bilateral, at the medial fat pad proximal to the joint line). A 2-down 1-up staircase method in which two positive ("yes") responses to the same stimulus are required move to the next lower stimulus value, and one negative response ("no") to move up to the next higher stimulus value was used. This procedure yields a 71% criterion level, as opposed to a chance level (i.e., 50%) that is obtained when one positive or negative response is sufficient to reverse the procedure. Blank trials were inserted on 20% of trials, in which the filament wa picked up and held near but without touching the subject. To shorten testing time, every third filament were applied until the first two positive responses to the same stimulus occurred, and then consecutively finer filaments were applied until one "no" response. After 5 stimulus value reversals, the last 4 were averaged to provide the threshold. (see Appendix 3)

2.2.9 Ischemic Pain Threshold

Ischemic pain threshold is usually assessed using the submaximal effort tourniquet test (SETT). In the SETT procedure, the participant is first asked to squeeze a dynamometer to their maximum strength using their non-dominant hand and their maximum grip is recorded. The participants is then instructed to lean back comfortably in a reclining chair and raise their dominant arm for 10 seconds to allow residual blood in

her arm to drain. The experimenter then places a blood pressure cuff around the participant's upper arm and inflates it to 200mm Hg and the participant is asked to squeeze an a dynamometer at 35% of their maximal grip with an intergrip interval of 2 seconds, that is, every 2 seconds until the pain becomes intolerable. An experimenter holding a stop watch signals the participants when to grip the dynamometer and records the exact times at which the participants verbally reports (1) the first sensation of pain (pain threshold) and (2) that the pain is intolerable (pain tolerance). (See Appendix 4)

In the present study, we used a modification of the SETT in which the dynamometer was replaced with an "anti-stress ball". The modification to the SETT was motivated by the fact that, after trying the procedure on fellow experimenters, we noticed that the majority of individuals had to stop before feeling any pain due to the numbness in their arm and fingers. Since the numbness was caused by the weight of the dynamometer, it was replaced with an "anti-stress ball". No other modifications were applied to the SETT procedure. The use of the submaximal effort tourniquet test (SETT) to induce ischemic pain is non-invasive, rapid and easy to administer. Moreover, this technique is widely used for assessing experimental pain in humans (Baron & Irving, 2002; Girdler & al,. 1998). Participants will also provide a subjective rating of the sensory and emotional component of the pain they felt. (See Appendices 5 and 6)

2.2.10 Capsaicin Inflammation (Skin reactivity)

Skin reactivity was measured by applying capsaicin to the skin and measuring the size of the flare. This is a non-invasive method to quantify substance P release in the skin. We used an adaptation of the method described by Helme and McKernan (1985). They applied 20 cl of capsaicin in 70% ethanol to 1 cm2 pieces of blotting paper to the upper forearm, covered the region with tape, and after 30 min traced around the visible flare and measured the area of the visible flare. Threshold for producing a flare was around 0.1 mg/ml, increasing to an asymptote around 10 mg/ml, with a reliable relationship between log dose and flare area. They also tested various other sites using 1 mg/ml, and found the largest responses on the trunk (10-15 cm2), with progressively

smaller responses at distal sites. Other studies in humans have also found that the threshold for evoking a flare was near or greater than 0.1 mg/ml (Andrews & al., 1999).

We used the following procedure: 2 rectangular areas on the upper back, 20 by 4 cm, separated by 3 cm on each side of the spine and centred just below the 7th cervical vertebra were outlined with a surgical pen. This region was chosen because some trials on ourselves with Zostrix (an over-the-counter preparation used to treat chronic pain) indicated that the sensation of heat was less here than on the arm or hand, and the flare was bigger. Capsaicin from natural sources (ie, concentrated from peppers) was obtained from SigmaAldrich, Canada Ltd. This contains approximately 65% capsaicin (trans-8methyl-N-vanillyl-6-nonenamide) and 35% dihydrocapsaicin; natural source capsaicin is used to prepare Zostrix (personal communication, Dr Chernegan, Research Director, GenDerm Ltd, Montreal). The material was weighed, and a stock solution 0f 100 mg/ml in 100% ethanol,stabilized with 10% Tween 80 (polyoxyethylene(20) sorbitan monooleate; generic name – polysorbate 80). Polysorbates vary according to the molecular weight of the lipid, and they are emulsifying agents commonly used in pharmaceuticals (parenteral, oral and topical formulations), cosmetics, foods and other substances requiring stable oil/water emulsions. The estimated acceptable daily intake of polysorbate esters is 12 mg/kg (FAO/WHO Expert Committee on Food Additives, 1974, cited in Renyolds et al., 1989 pp 1246-1247). The stock solution was further diluted and mixed with proprietary ointment base (ie, paraffin based cream; these creams usually contain soft paraffin, paraffin oil, a sterol alcohol, and, sometimes purified beeswax, cholesterol and/or polysorbate) with similar properties to that used in preparation of Zostrix. Concentrations were spaced at log to the base 3 intervals ranging from 2 mg/ml to 0.008 mg/ml (i.e. 2, 0.67, 0.22, 0.07, 0.02, 0.008). The resulting creams were spread evenly onto 0.5 cm in diameter disks of filter paper, thin enough that it did not squeeze out the edges when pressed. The disks were applied in an evenly spaced row within the rectangles marked on the participant's back. That is, 6 disks were placed on each rectangle. The different concentrations of capsaicin were placed in inverse order (i.e. strongest to lowest and lowest to strongest) on either side of the spine. The row of paper disks was covered with plastic wrap and easily removable tape. During the 20 min period

of exposure of the skin to the capsaicin cream, the interview on eating habits was performed.

After 20 min had elapsed, the tape was removed and the flare was traced on a transparency. The area was then wiped gently with 70% ethanol (capsaicin is soluble in ethanol), and then, by a damp towel to remove any residual cream. The images were coded so that analysis was done blind to the group identity of the subject. For analysis, the transparencies were scanned, the sizes of the flares were calculated in pixels and the pixels were entered as pharmacological responses to the different capsaicin concentrations. Slope, minimum effect, maximum effect and median effective dose (ED50) were then extracted for each participant. No participants reported any pain following capsaicin application.

2.2.11 Autonomic function

Autonomic function was assessed by changes in heart rate variability (HRV) and blood pressure (BP), following induction of an orthostatic challenge. These autonomic function tests are non-invasive, are relatively easy to administer, and provide quantitative information about autonomic function under controlled conditions. Upon arrival in the laboratory, an automatic blood pressure monitor (IntelliSense Monitor, Ormron Healthcare Inc.) and a portable heart rate monitor (Polar S810, Polar Electro Oy) was applied. Beat-to-beat (R-R) intervals were obtained using a chest band with the recorder mounted around the wrist while BP was sampled at key times using the auto-inflation cuff. Automatic blood pressure monitors show little measurement drift with manual recording, and have been shown to compare well to intraarterial blood pressure readings. During the time when participants sit quietly while answering a brief set of questionnaires (20 minutes); baseline HR was recorded and BP was established. BP were taken once every 5 minutes during this period, not counting the first 5 minutes, while HR was recorded continuously. (see Appendix 7, part 1)

Following completion of the questionnaires, subjects underwent an orthostatic challenge. Participants first rested in a supine position for 4 minutes; BP and HR was taken 2 minutes after the participant had assumed the position, and at 4 minutes. After 4

min, the participants stood, and BP was immediately recorded and recorded again every 2 minutes for a period of 4 min. HR was recorded continuously throughout the procedure. (see Annex 7, part 2) Orthostatic hypotension is defined as the occurrence of a postural decrease in BP of 20mm Hg for at least 3-4 min (Hoeldtke & Streeten, 1993; Engstrom & Aminoff, 1997). A variety of non-neurogenic aetiologies may cause orthostatic hypotension, but this is generally accompanied by a compensatory increase in HR. The increase in HR does not occur in patients with neurogenic causes of orthostatic hypotension (Engstrom & Aminoff, 1997).

CHAPTER 3

RESULTS

3.1 Participant's Classification and Demographic Characteristics

23 ED patients and 16 Controls were recruited (N = 39). No participants were excluded from data analysis, although there was missing data for some participants on some measures. This was handled by excluding participants with missing data on the specific analyses. Details about exclusion are specified in each section.

16 participants did not suffer from an ED and were classified as controls. 17 ED patients had a diagnosis of AN according to the DSM-IV prior to starting treatment and were placed into the AN patient group. At the time of testing, 3 AN patients were normal weight (BMI > 18). Within the AN patient group, 7 patients were placed into the AN *restrictive subtype* group and 10 patients were placed into the AN *binge-eating/purging subtype* group. The *AN restrictive* subtype applies to the AN patients who 1) accomplish weight lost primarily through dieting and fasting and/or excessive exercise and 2) do not engaged regularly in binge eating or purging. *AN binge-eating/purging* subtype refers to the AN patients who regularly engage in binge-eating and/or purging (DSM-IV). 6 ED patients had a diagnosis of BN according to the DSM-IV prior to starting treatment and were placed into the BN patient group. At the time of testing, 1 BN patients had been free of binge/purge episodes for more than 3 months. Due to the small number of patients included in this group (n = 6), the BN patients group was not further divided into subtypes. This is further justified by a study by Walters & al. (1993) which reported that the two BN subtypes did not differ substantially on their demographic characteristics, weight and personality. Details about treatment and diagnosis are presented in the section 2.1of Methods and Material.

Demographic characteristics for each group (i.e. AN patients with Restrictive Subtype, AN patients with Binge/Purge Subtype, BN patients and Controls) are presented in Table 2. Analysis of Variance (ANOVA) yielded a significant difference between the 4

groups for Body Mass Index ($F(3,38) = 12.4$; $p < 0.01$). Least Squares Difference (LSD) post-hoc comparisons revealed that both AN patients group (i.e. Restrictive and Binge/purge Subtypes) had a significantly lower BMI than BN patients and Controls. Data suggests young women comprised the majority of the overall sample. Consistent with the literature, the BMI's of BN patients were generally in the normal weight range (Steiger & Bruce, in review; Walsh, Wheat & Freund; 2000) while AN patients suffering from both subtypes were seriously underweight (see Table 2). It should be noted that controls, while still exhibiting normal BMIs (i.e. BMI $\geq$ 18.5), are fairly thin. The recruitment of controls through advertising at McGill University and through the snow-ball method (see Methods) might have influenced the selection of controls toward thinner women. Specifically, young university women are by and large slim and active. It is also possible that controls recruited through the snow-ball method are likely to share similar environment and beliefs with their friend suffering from an ED and while not presenting the symptoms of an ED themselves, might still be more concerned about their weight than other women. By comparing ED patients with slim controls, we reduced the probability that results reflect differences in BMI's or body types instead of true underlying physiological discrepancies.

ANOVA also yielded a significant difference between the groups for Level of Education. ($F= (3, 38)= 3.1$; $p < 0.05$). LSD post-hoc comparisons revealed that BN patients were significantly less educated than Controls ($p < 0.05$).

Demographic data presented as proportions (Table 2) were analyzed using Chi-Square to test for significant differences between groups. Missing data for each group is specified in Table 2. For cigarette use, the proportion of smokers in AN patients with Binge/Purge Subtype was significantly higher than observed in all other groups; that is, higher than controls, AN patients with Restrictive Subtype and BN patients ($x^2= 12.8$, $p < 0.01$; $x^2= 4.94$, $p < 0.05$; and $x^2= 4.01$, $p < 0.05$ respectively). For vitamin intake, the proportion of individuals taking vitamins regularly is noticeably larger in AN patients with Restrictive Subtype than the proportions observed in all the other groups; that is, larger than controls, AN patients with Binge/Purge Subtype and BN patients ($x^2= 6.6$, $p < 0.05$; $x^2= 7.1$, $p < 0.51$; and $x^2= 18.8$, $p < 0.01$ respectively). For pain medication intake, the proportion of individuals taking pain medication regularly (see Table 2 for specific

criteria) was significantly higher in AN patients with Binge/Purge Subtype and BN patients when compared with controls ($x^2 = 8.0$, $p < 0.01$; and $x^2 = 5.6$, $p < 0.05$ respectively). ED groups also differed from each other. Specifically, the proportion of AN patients with Restrictive Subtype taking pain medication regularly was noticeably lower when compared to AN patients with Binge/Purge Subtype and BN patients ($x^2 = 11.6$, $p < 0.01$; and $x^2 = 8.2$, $p < 0.00$ respectively). For pain-related physician visits (see Table 2 for specific criteria), no significant differences were found between groups. Recent recreational drug use was low in all groups.

A general classification of medication intake for each group is presented in Table 3. Overall, 13/23 patients were taking psychotropic medications and the medications were highly varied. Results from statistical analyses exploring the effects of medications on the different health and sensory measures are presented in section 3.9.

Table 2. Demographic Characteristics in AN patients[14] with Restrictive Subtype, AN patients with Binge/Purge Subtype, BN patients[15] and Controls.

Participant's Group; Mean Score ± Std. Dev. or Proportion				
	Control	**AN patients: Restrictive Subtype**	**AN patients: Binge/Purge Subtype**	**BN patients**
N	16	10	7	6
Age	22.8 ± 5.0	22.3 ± 4.8	28.7 ± 10.4	24.7 ± 2.9
Body Mass Index[16]	20.3 ± 1.4	16.0 ± 2.3 **	17.2 ± 1.8 **	22.6 ± 4.7‡⫿⫿
Education Level[17]	2.6 ± 0.6	2.4 ± 0.5	2.1 ± 0.4	1.8 ± 0.8 **
Exercise Frequency [18]	2.3 ± 1.2	2.2 ± 1.1	2.3 ± 1.3	2.7 ± 1.2
Cigarette use[19]	2/16	2/9$^{\Delta}$	4/7 **†	1/6 ⫿
Vitamin intake[20]	11/16	8/9$^{\Delta}$ *	4/7 †	2/6 ‡
Recreational drug use[21]	2/16	1/9$^{\Delta}$	0/7	0/6
Pain medication use[22]	4/16	2/10	5/7 *‡	4/6 *‡
Pain-related Physician visits[23]	7/15$^{\Delta}$	4/10	4/7	3/6

* $p < 0.05$; ** $p < 0.01$ relative to the Control

† $p < 0.05$; ‡ $p < 0.01$ relative to the AN Restrictive Subtype group

⫿ $p < 0.05$; ⫿⫿ $p < 0.01$ relative to the AN Binge/Purge Subtype group

$^{\Delta}$Missing data for one participant

[14] ED patients were placed into the AN group according to the criteria: Diagnosis of AN according to the DSM-IV prior to starting treatment. The *AN Binge/Purge* Subtype applies to the AN patients who regularly engage in binge-eating or purging while the Restrictive Subtype applies to the AN patients who accomplish weight lost primarily through dieting fasting and/or excessive exercise.

[15] ED patients were placed into the BN group according to the criteria: Diagnosis of BN according to the DSM-IV prior to starting treatment. One (1) BN patient did not have any binge/purge episodes for 3 months or more prior to the time of testing.

[16] Calculated as: weight (kg)/ height² (m²)

[17] Rated using a 1-4 scale: (1- High school; 2- Cegep or equivalent; 3- University: Bachelor or equivalent; 4-University: Graduate school)

[18] Rated using a 0-4 scale: (0- never; 1- rarely; 2- weekly; 3- several times a week; 4- daily)

[19] Proportion of individuals that answered yes on the question: Do you smoke cigarettes?

[20] Proportion that self-reported taking vitamins on a regular basis

[21] Proportion that consumed recreational drugs (marijuana, cocaine, etc) in the last 30 days

[22] Proportion that take ≥ 2 doses of over-the-counter analgesics in a typical month.

[23] Proportion that have ever visited a physician for one of the pain problems listed in the questionnaire (from a list of 19 pains)

Table 3. Medication Intake in Eating Disorder patients and Controls.

Participant's Group; Proportion				
	Control	**AN patients: Restrictive Subtype**	**AN patients: Binge/Purge Subtype**	**BN patients**
Medication Intake: ***Any Medication***[24]	**2/16**	**4/10**	**5/7**	**6/6**
Medication Intake: ***Multiple Medications***[25]	**0/16**	**1/10**	**4/7**	**3/6**
Serotonergic Medication: Citalopram; Paroxetine; Fluoxetine; Trazodone[26]	0/16	3/10	5/7	3/6
Major tranquilizers: Olanzapine[27]; Quetiapine[4;]	0/16	1/10	3/7	3/6
Medical Condition: Alendronate sodium[28]; Allergy medication; Asthma medication; Iron Supplement; Metoclopramide [29]; Pantoprazole[30]; Sevelamer hydrochloride[31]; Thyroid hormones[32]	2/16	1/10	3/7	3/6
Sleep Medication: Miscellaneous prescription and OTC sleeping aids	0/16	1/10	2/7	4/6
Miscellaneous: Clonazepam[10] Bupoprion[33]; Lamotrigine[11] Lithium[11]	0/16	0/10	2/7	1/6

[24] Proportion of individuals taking any medication at the time of testing
[25] Proportion of individuals taking >1 medication at the time of testing.
[26] Antidepressant, anxiolytic, and hypnotic properties
[27] Atypical antipsychotic
[28] Oasteopososis medication
[29] Antiemetic and gastroprokinetic agent
[30] For gastroesophageal reflux disease
[31] Controls serum phosphorous
[32] Stable for more than a year
[33] For mood and anxiety disorders

3.2 General Health

Figure 1 shows mean scores for each group for General Mental Health and General Physical Health, as measured by the SF-36; as well as means scores for each group on the eight subscales of the SF-36. Scores are expressed using a 0-100 scale, where 0 indicates gross impairment and 100, perfect functioning. One participant from the AN-Restrictive Subgroup was excluded from data analysis due to missing data. Scores on the SF-36 for the controls are, overall, consistent with SF-36 normative data on 12-24 year old Canadian women, with Role-Emotional scores being slightly lower in the controls than what would be expected (see Hopman et al., 2000). Specifically, controls showed mean scores (Mean ± SD) of 60.4 ± 44.3 instead of 77.6 ± 35.3. As in the case of BMIs, the slightly lower scores on Role-Emotional might be, to a certain extent, due to the recruitment method which favored the selection of friends of women suffering from EDs as controls (see discussion on BMIs in section 2.1 for a more in-depth explanation).

For the 8 subscales of the SF-36, scores on varied substantially across participants with mean scores on Physical Functioning and Bodily Pain being noticeably higher than mean scores on Vitality and Role-Emotional (Figure 1). Repeated Measure ANOVA revealed an overall significant difference between groups ($F= (3,34) = 6.7$ $p < 0.01$) and significant differences on four of the eight subscales: Role-Physical[34], Vitality[35], Social Functioning[36] and Mental Health[37]. Besides for the Vitality scale, where only the AN patients with Binge/Purge Subtype significantly differed from controls ($p < 0.01$), both AN patients groups were significantly lower than controls on all scales mentioned above ($p < 0.01$ for all, besides Role Physical[38]). Also, BN patients had significantly lower scores than controls on both the Mental Health and Social Functioning scales ($p < 0.01$ for both).

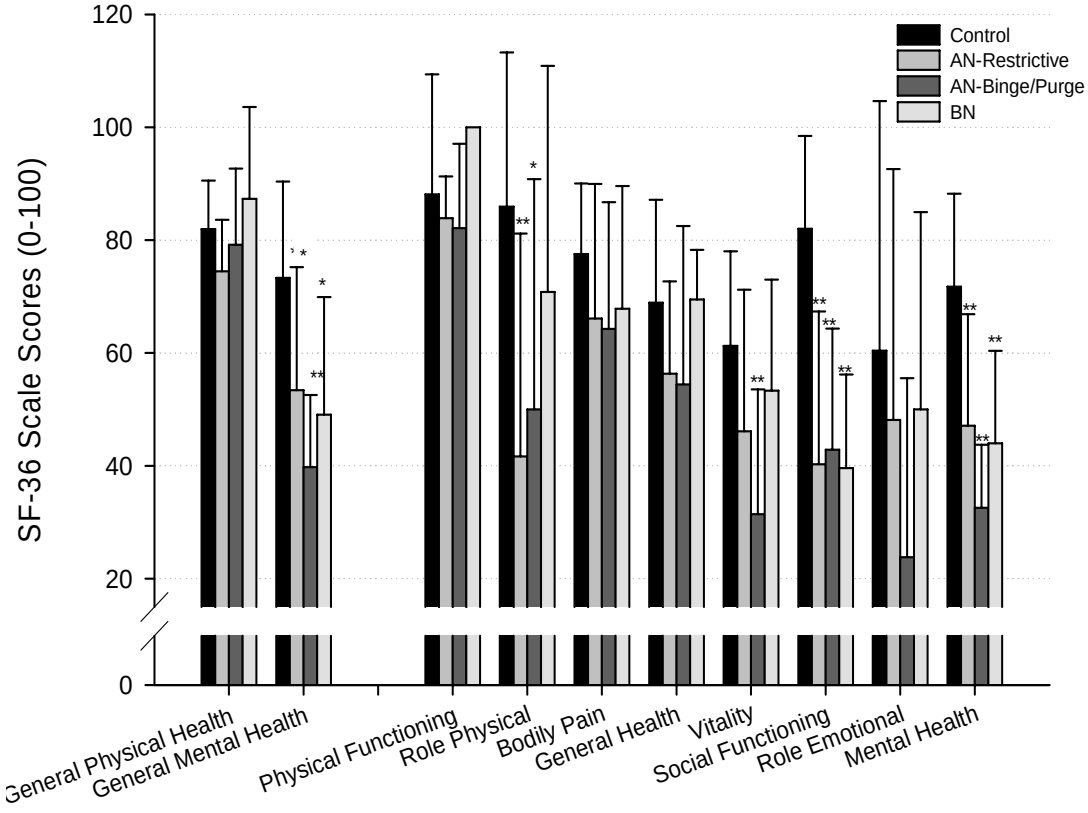
ANOVA revealed a significant difference between groups for General Mental Health ($F(2,37)= 7.6$, $p < 0.01$). LSD post-hoc comparisons showed that controls had significantly higher mental health functioning when compared with all ED patient groups.

[34] $F (2,37) = 3.7$, $p < 0.05$
[35] $F(2,37)= 3.7$, $p < 0.05$
[36] $F(2,37)=12.7$, $p< 0.01$
[37] $F(2,37)= 11.3$, $p < 0.01$
[38] $p < 0.05$ for AN patients with Binge-Purge Subtype relative to controls

Specifically, controls showed considerably higher Mental Health scores than AN patients with Restrictive Subtype AN patients with Binge/Purge Subtype; and BN patients ($p < 0.05$; $p < 0.01$; and $p < 0.05$, respectively). Surprisingly, no difference was found between groups for General Physical Health.

In other words, data suggest that ED patients in treatment experience normal/good physical health, but suffer marked impairment in terms of their general mental health and their capacity to maintain functioning.

Figure 1. SF-36 Mean Scores (Mean ± SD) for Eating Disorder patients and Controls.



* p < 0.05; ** p < 0.01 relative to the Control

3.3 Psychopathologies

Figure 2 shows the Global Severity Index (GSI) and the Positive Symptom Distress Index (PSDI) of the SCL-90-R for each group. The GSI measures overall psychological distress and is rated as the mean distress rating on all 90 items (0-100). The PSDI measures the intensity of the symptoms and is rated as the mean distress of all 90 items not rated as zero (0-100). Participants were all included in data analysis. ANOVA yielded significant differences for both the GSI and the PSDI ($F(3,38)= 22.2$, $p < 0.01$; and $F(3,38)= 25.0$, $p < 0.01$, respectively). LSD post-hoc comparison revealed that overall psychological distress (as rated by the GSI) and symptom intensity (as rated by the PSDI) were both considerably lower in controls when compared to all ED patient groups. Specifically, controls were significantly less distressed than AN patients with Restrictive Subtype ($p < 0.01$), AN patients with Binge/Purge Subtype ($p < 0.01$) and BN patients ($p < 0.05$). Also, controls had significantly less psychopathology symptoms than AN patients with Binge/Purge Subtype, and to a lesser extent, than AN patients with Restrictive Subtype and BN patients ($p < 0.01$ for all).

Figure 3 shows mean scores on the nine primary dimension scales of the SCL-90-R for each group. Scores are presented as a percentage of symptom severity (0-100), where 0 indicates the absence of symptom and 100 indicates the presence of all symptoms at maximum intensity. Repeated Measures ANOVA revealed an overall significant difference between the 4 groups on psychopathologies ($F(3, 35)= 18.3$, $p < 0.01$) and significant differences on seven of the nine primary symptoms dimensions ($p < 0.01$ for all) : Somatization (F[39] $= 7.7$), Obsessive-Compulsive ($F = 9.4$), Interpersonal Sensitivity ($F = 19$), Depression ($F = 22.1$), Anxiety ($F = 6.9$) Phobic Anxiety ($F = 11.3$) and Psychoticism ($F = 10.7$). LSD post-hoc comparisons were performed to determine which groups differed from each other.

For Somatization, AN patients with Binge/Purge Subtype and to a lesser extent, AN patients with Restrictive Subtype ($p < 0.01$; and $p < 0.05$, respectively) reported meaningfully more symptoms that controls. Also, AN patients with Binge/Purge Subtype reported significantly more somatization symptoms than BN patients ($p < 0.05$).

[39] df = 3,38 for all subscales

For Obsessive-Compulsiveness, AN patients with Binge/Purge Subtype, and to a lesser extent, AN patients with Restrictive Subtype reported markedly more symptoms than controls ($p < 0.01$ for both) and BN patients ($p < 0.05$ and $p < 0.01$, respectively).

For Interpersonal Sensitivity, controls reported distinctively fewer symptoms when compared to all ED patients groups. Specifically, AN patients with Binge/Purge Subtype showed the highest level of Interpersonal Sensitivity symptoms ($p < 0.01$) , followed by the AN patients with Restrictive Subtype ($p < 0.01$) and BN patients ($p < 0.01$). Also, BN patients and, to a lesser extent, AN patients with Restrictive Subtype reported significantly less symptoms on the Interpersonal Sensitivity dimension than AN patients with Binge/Purge Subtype ($p < 0.01$ and $p < 0.05$, respectively)

For Depression, controls reported distinctively fewer symptoms when compared to all ED patients groups. Specifically, AN patients with Binge/Purge Subtype showed the highest levels of symptoms followed by the AN patients with Restrictive Subtype and BN patients ($p < 0.01$ for all). Also, AN patients with Binge/Purge Subtype reported significantly more depressive symptoms than the other patient groups; that is, more than AN patients with Restrictive Subtype and BN patients ($p < 0.01$ for both)**.**

For Anxiety symptoms, controls reported significantly fewer symptoms than AN patients with Binge/Purge Subtype and, to a lesser extent, AN patients with Restrictive Subtype ($p < 0.01$; and $p < 0.05$, respectively). Although mean score on the anxiety dimension of the BN patients represented almost twice the mean score of controls, the difference was not significant ($p > 0.2$). Also, AN patients with Binge/Purge Subtype reported significantly higher levels of anxiety than the other patients groups; that is, than BN patients and AN patients with Restrictive Subtype ($p < 0.05$ for both).

For Phobic Anxiety symptoms, AN patients with Binge/Purge Subtype reported markedly more symptoms when compared to controls and the other ED patients groups. The least report of phobic anxiety was from controls, followed by BN patients and AN patients with Restrictive Subtype ($p < 0.01$ for all).

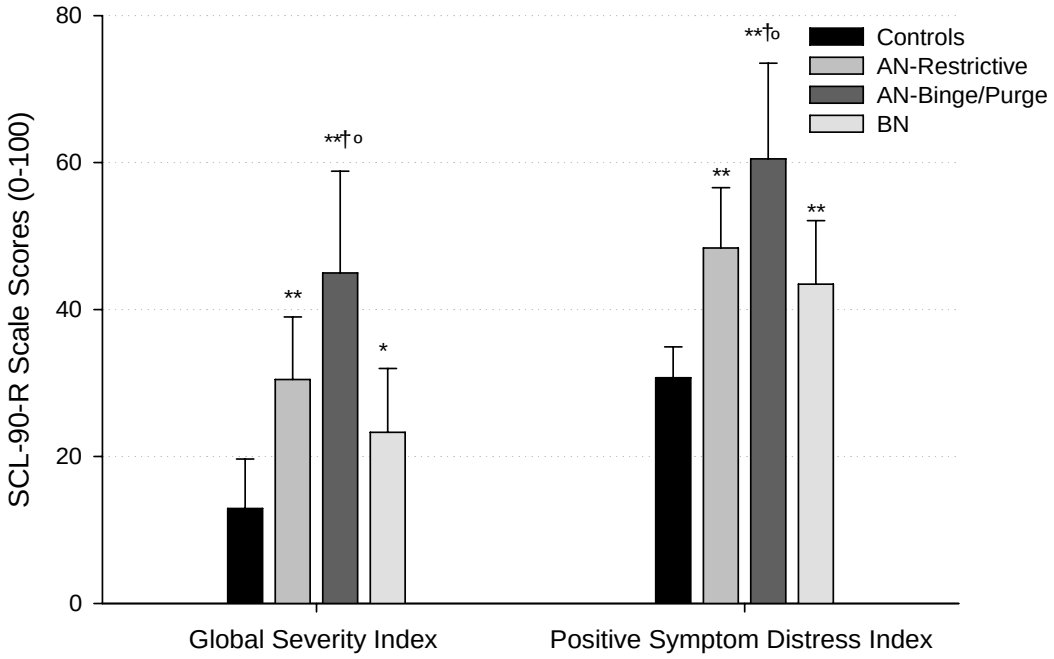
For Psychoticism, controls reported significantly fewer symptoms than AN patients with Binge/Purge Subtype and AN patients with Restrictive Subtype ($p < 0.01$ for both). Although mean score on the psychoticism dimension for BN patients represented almost twice the mean score of controls, the difference was far from

significant ($p > 0.3$). BN patients also reported significantly less symptoms than AN patients with Binge/Purge Subtype and AN patients with Restrictive Subtype ($p < 0.01$; and $p < 0.05$, respectively).

Our results are consistent with the literature on EDs and their associated psychopathologies. (Gadalla, 2008; Godart & al.,2007; Steiger & Bruce, 2004). It is also noteworthy that AN patients with Binge/Purge Subtype exhibited higher symptomatology on all nine psychopathology dimensions, as well as higher levels of general distress (i.e. GSI) and symptom intensity (i.e. PSDI). These results suggest AN patients with Binge/Purge Subtype suffer the highest levels of psychological and emotional impairments when compared to other ED patients and are supported by similar findings in the literature on AN (Herzog & al., 1999).

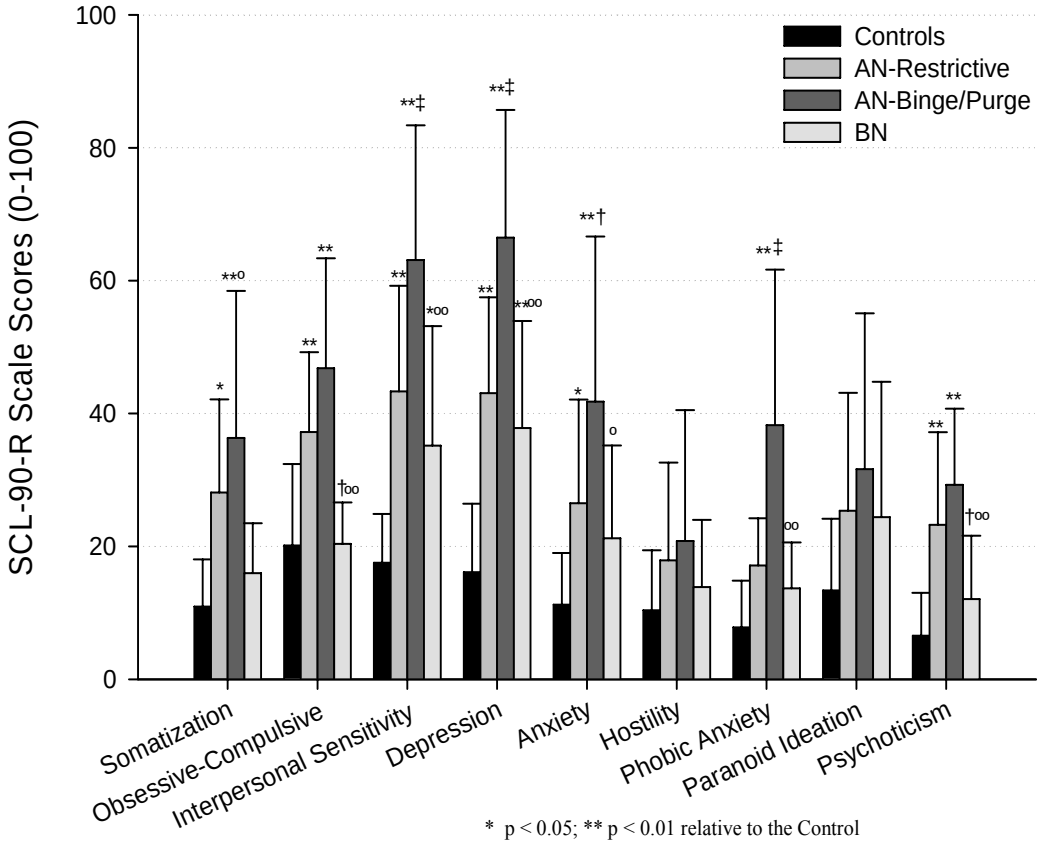
Also, even though mean symptom scores of BN patients were almost double those of controls on the majority of the nine SCL-90-R symptom dimensions, differences between BN patients and controls only reached significance on 2 of the dimensions: Interpersonal Sensitivity and Depression. This, however, does not imply that BN patients do not suffer from important mental health impairments since data also shows that BN patients are much more elevated when compared to controls on overall psychological distress (as rated by the GSI) and overall symptom intensity (as rated by the PSDI). Overall, data imply that Binge/Purge Disorders (i.e. BN and AN-Binge/Purge Subtype) are associated with an array of mental health impairments rather than a few specific ones, while Restrictive Disorders are associated with a more homogeneous profile of psychopathologies.

igure 2. SCL-R 90 Mean Scores (Mean ± SD) on the General Severity Index and Positive Symtptor
)istress Index for Eating Disorder patients and Controls



* p < 0.05; ** p < 0.01 relative to the Control
† p < 0.01 relative to the AN Restrictive Subtype group
º p < 0.01 relative to the AN Binge/Purge Subtype group

Figure 3. SCL-90-R Primary Dimensions Symptoms Scores (Mean ± SD) for Eating Disorder patients and Controls



* $p < 0.05$; ** $p < 0.01$ relative to the Control

† $p < 0.05$; ‡ $p < 0.01$ relative to the AN Restrictive Subtype group

º $p < 0.05$; ºº $p < 0.01$ relative to the AN Binge/Purge Subtype group

3.4 Depression and Anxiety

Figure 4 shows scores on the Depression and Anxiety Scales of the HADS, which excludes items reflecting common somatic symptoms accompanying depression and anxiety. Scores indicate symptom severity and are rated using a 0-21 Scale, with 0 indicating the absence of symptoms, and 21, severe clinical anxiety and/or depression. All participants were included in data analysis.

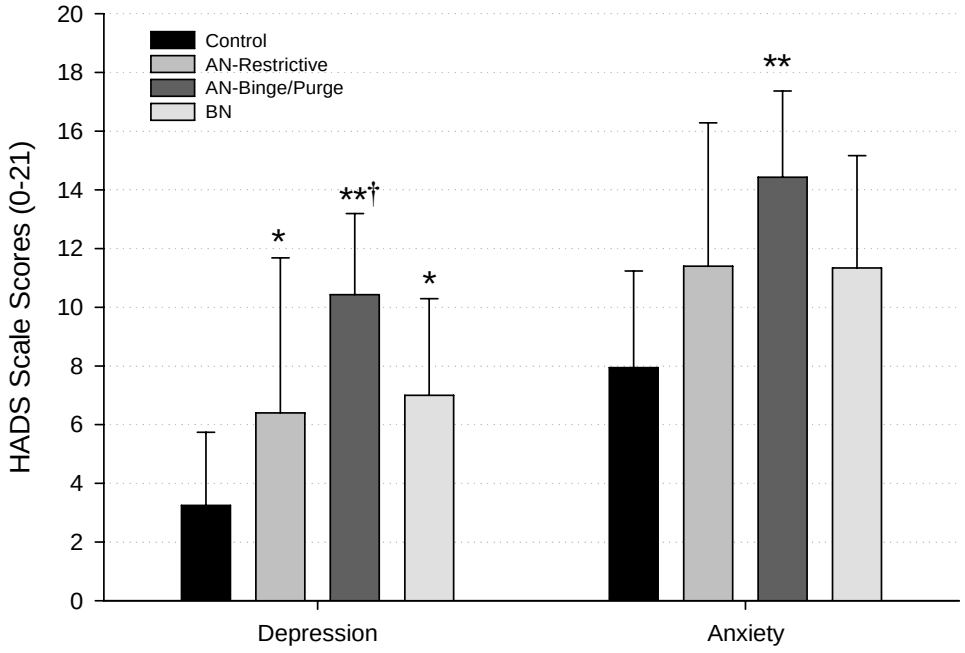
Repeated Measure ANOVA yielded a significant difference between the 4 groups for both depression and anxiety scores on the HADS ($F(3,34)= 10.7$, $p < 0.01$). For Anxiety, LSD post-hoc comparison revealed that AN patients with Binge/Purge Subtype were significantly more anxious than controls ($p < 0.01$). Although not reaching significance, LSD also showed that AN patients with Restrictive Subtype and BN patients were more anxious than Controls ($p > 0.07$ for both); and that AN patients with Binge/Purge Subtype were more anxious than AN patients with Restrictive Subtype ($p > 0.07$).

For Depression, LSD post-hoc comparison revealed that controls were significantly less depressed when compared to ED patients groups. That is, controls were considerably less depressed than AN patients with Restrictive Subtype, AN patients with Binge/Purge Subtype and BN patients ($p < 0.05$, $p < 0.01$ and $p < 0.05$ respectively). Also, AN patients with Binge/Purge Subtype tended to be more depressed than AN patients with Restrictive Subtype ($p < 0.05$). Finally, consistent with recent statistics of mental illnesses prevalence in Canadian population[40], anxiety and depression symptoms were somewhat common in both ED patients and non-ED participants

Overall, results suggest that depression and anxiety symptoms were both markedly elevated in women suffering from EDs. This is consistent with current knowledge of high co-morbidity between anxiety and depression disorders and EDs (Braun, Sunday & Halmi, 1994; Gadalla, 2008; Goossens & al., 2009). Finally, data also suggests that, by and large, AN patients suffering from Binge/Purge Subtype are the most distressed of all ED patients groups.

[40] See Health Canada; *A Report on Mental Illnesses in* Canada (2002)

Figure 4. HADS Depression and Anxiety Scale Scores (Mean ± SD) for Eating Disorder patients and Controls.



* $p < 0.05$; ** $p < 0.01$ relative to the Control

† $p < 0.05$ relative to the AN Restrictive Subtype group

3.5 Aches and Pains

Aches and Pains complaints were assessed using a list of 19 commonly experienced pains, with frequency and severity being recorded for each pain. Frequency was rated using a 0 to 3 points scale, with 0 representing no pain or pain felt little of the time, and 3, pain felt most of the time. Severity was rated using a 1 to 3 points scale, with 1 representing low pain and 3, strong pain. An Overall Pain Complaints Score and an Overall Pain Distress Score; as well as specific pain scores for each pain (19 all together) were computed. The Overall Pain Complaints Score represents the intensity of aches and pains and is calculated using pain frequency on all 19 pains. The Overall Pain Distress Score is a "pain index", such as is frequently used to describe headaches and is computed as frequency multiplied by severity for each category of pain.

Contrary to expectations, ED patients did not differ from controls on Overall Pain Complaints or on Overall Pain Distress. However, ANOVAs performed each of the 19 pains separately revealed a significant difference between groups on four of the 19 pains recorded: Bloating or Gas Pain ($F(3,38)= 5.3$, $p < 0.01$); Painful constipation ($F(3,38)= 4.2$, $p < 0.05$); Tension Headaches ($F(3,38)= 4.2$, $p < 0.05$) and Migraines ($F(3,38)= 3.5$, $p < 0.05$). Figure 5 shows means frequency scores for Bloating or Gaz Pain, Painful constipation, Tension Headaches and Migraines; as well as mean overall pain complaints for all groups. Other pains are not shown for clarity purposes.

LSD Post-hoc comparisons showed that Controls reported significantly less Bloating or gaz pain when compared to all patients groups[41]. Predictably, painful constipation was significantly lower in controls than both patients groups with Binge/Purging behaviors, that is, the AN patients with Binge/Purge Subtype and BN patients ($p < 0.01$ and $p < 0.05$, respectively). AN patients with Binge/Purge Subtypes reported the highest levels of head pains (i.e. tension headaches and migraines) when compared the other ED patients and controls. In terms of significant differences, analyses showed that AN patients with Binge/Purge Subtype reported considerably more tension headaches and more migraine-type headaches than both the AN patients with Restrictive

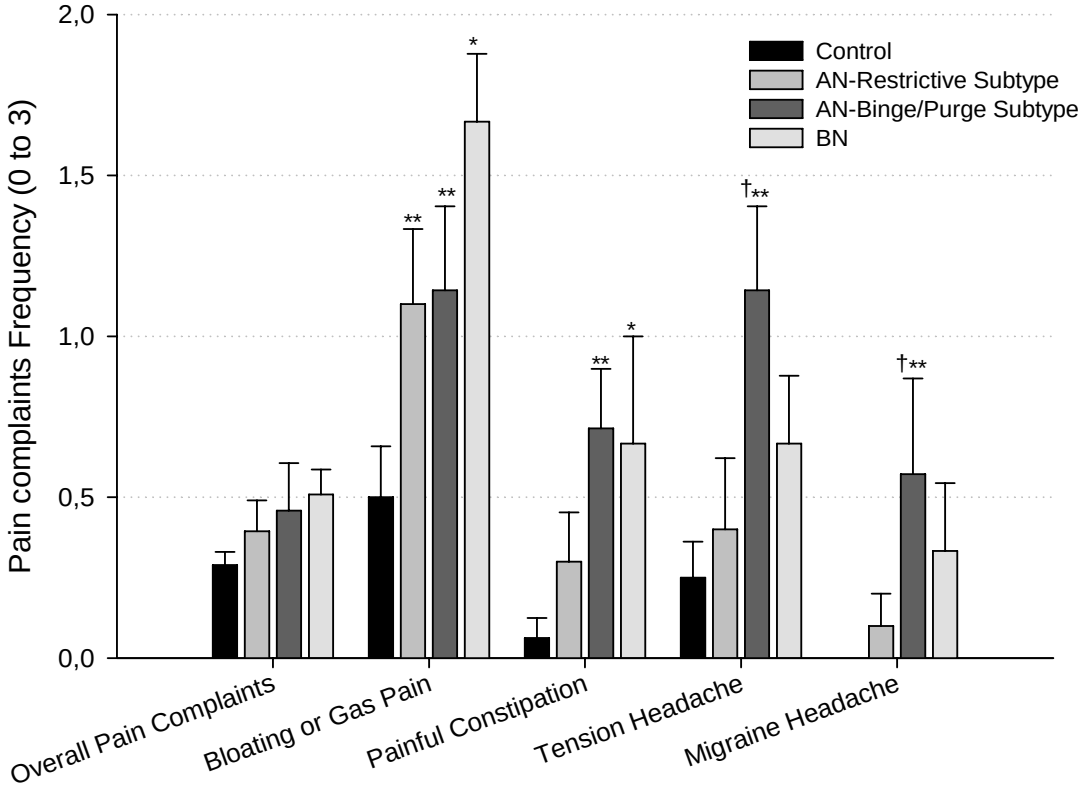
[41] $p < 0.05$ for both AN patients groups and $p < 0.01$ for BN patients.

Subtype and the controls[42] ($p < 0.05$; and $p < 0.01$, respectively for both tension headaches and migraines).

Overall, data on commonly experienced aches and pains suggest ED patients are normal in terms of general pain experience, but suffer from specific pains that are likely to relate to their eating-disordered behaviors; for example, painful constipation and chronic laxative use. Relationships between specific ED behaviors and/or symptoms are explored in section 3.10.

[42] None of the controls reported suffering from migraines.

Figure 5. Mean Overall Pain Complaints (Mean ± SE) and Mean Reports (Mean ± SE) of Four Commonly Experienced Aches and Pains in Eating Disorder patients and Controls.



* p < 0.05, ** p < 0.01 relative to the Control
† p < 0.05 relative to the AN Restrictive Subtype group

3.6 Pain Sensitivity

Pain sensitivity was assessed using a broad range of methods. Specifically, pains measures included pressure pain thresholds 1) on the non-dominant hand and 2) over the body; and ischemic pain threshold and tolerance. All measures of pain sensitivity correlated positively with each other[43], except that pressure pain thresholds over the body and ischemic pain thresholds did not appear to be closely related to each other ($p > 0.1$).

The highest correlation was found between ischemic threshold and tolerance ($r = 0.6$, $p < 0.01$), followed by the two measures of pressure pain thresholds[44] ($r = 0.54$, $p < 0.01$). Results are consistent with current understanding of pain sensitivity. Specifically, different types of pain and/or tissue stimulations (e.g. pressure vs heat and/or deep somatic tissues vs cutaneous tissue) are related and thus, are all indicators of general pain sensitivity, but are not interchangeable. Also, the more similarities between the methods used elicit pain or the types of nociceptors[45] activated, the more correspondence there is. (See introduction for an in-depth discussion of pain sensitivity)

3.6.1 Pressure Pain Thresholds over the Hands

Figure 6 shows mean pain thresholds over the Hand. Thresholds were measured on the non-dominant hand and averaged across all five fingers. Two participants from the control group were excluded due to missing data. ANOVA yielded a significant difference between groups for Pain Thresholds over the Hands ($F(3,36) = 3.3$, $p < 0.05$). LSD post-hoc comparisons showed that BN patients have higher pain thresholds on the hands than AN patients with Restrictive Subtype and Controls ($p < 0.05$; and $p < 0.01$, respectively). Other ED groups did not differ from each other or the Controls, although there was a tendency for BN patients to show higher PPT on the hands when compared to AN patients with Binge/Purge Subtype ($p > 0.06$) ANCOVA revealed that the difference between the groups on hand PPT was still significant after controlling the effect of BMI, blood pressure and exercise frequency ($F(3, 36) = 6.0$, $p < 0.01$).

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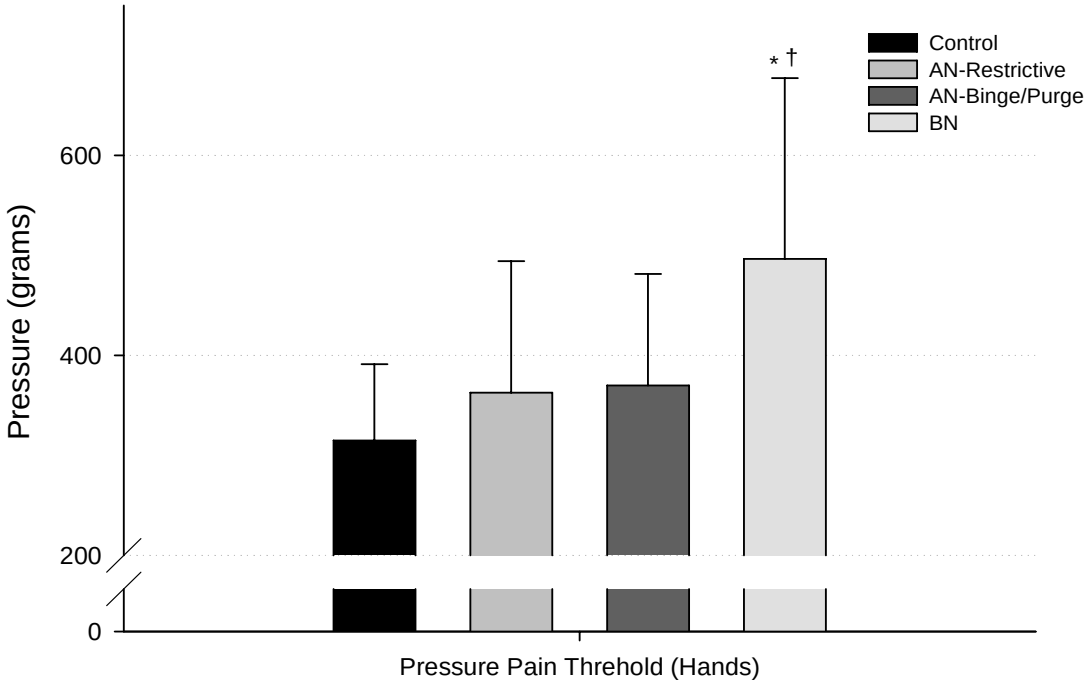
[43] $r \geq 0.33$, $p < 0.05$ at least

[44] That is, pressure pain threshold over the hand and pressure pain threshold over all four quadrants

[45] Sensory receptors specific to pain stimuli

Results suggest that BN patients have higher PPT on the hands not only when compared to non-ED patients but also when compared to AN patients with Restrictive Subtype. In light of this, one could theorize that binge/purge behaviors underlines the increased pain sensitivity observed in some ED patients. Data, however, does not support the existence of a meaningful relationship between binge/purging behaviors and hand PPT (see section 3.10). Taking these facts into account, results support that BN patients differ in their pain sensitivity from AN patients with Restrictive Subtype for reasons other than variations in binge/purge behaviors. Also worth pointing out is the fact that the variance within the Control group was lower by about half than the variances within the different ED groups. This suggest that ED patients, regardless of their specific diagnostic (i.e. AN Restrictive, AN Binge/Purge, BN), constitute a highly heterogeneous population in terms of pain sensitivity relative to the Controls.

Figure 6. Pressure Pain Threshold on the Hand (Mean ± SD) for Eating Disorder patients and Controls.



* p < 0.01 relative to the Control

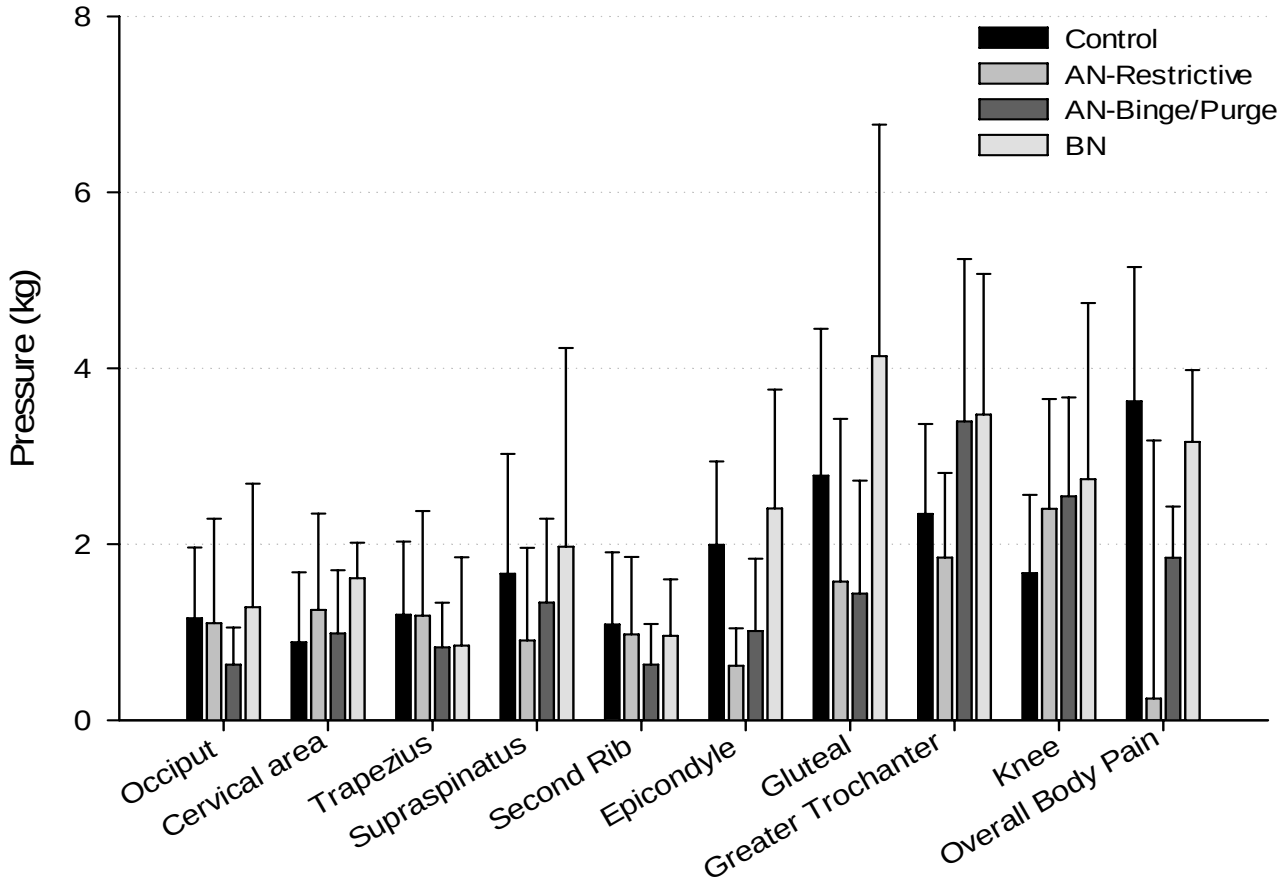
† p < 0.01 relative to the AN Restrictive Subtype group

3.6.2 Pressure Pain Thresholds (across all four quadrants)

Figure 7 shows mean pressure pain thresholds over the body for each group. Pressure pain thresholds on the left and right side were averaged (see Methods) and data are expressed in kg. All participants were included in data analysis. One control, however, was missing 1 data point on the gluteal area. Mean pain thresholds varied substantially across participants as well as the different body sites, with participants showing the lowest sensitivity at the greater trochanter and gluteus (i.e. higher pain pressure thresholds) and the highest sensitivity at the second rib, occipitut and trapezius.

No significant difference was found with Repeated Measures ANOVA across all 9 sites tested, but there was a trend for BN patients to show slightly elevated pressure pain thresholds over the body when compared to the other groups ($F(3,34)= 2.44$, $p > 0.08$). Since individuals with more lean muscles and/or fat tissue have higher BMIs; and since the amount of pressure required to elicit pain (i.e. pressure pain threshold) is greater when there are more tissues to compress, the relationship between BMIs and body PPT was explored using Pearson's correlation. A positive correlation between BMIs and overall pressure pain threshold over the body ($r = 0.40$, $p < 0.05$) was found. Because patients with BN tended have slightly higher BMIs than all other groups, we believe that the trend for BN patients to show elevated pressure pain thresholds over the body may reflect differences in BMIs rather than a genuine underlying physiological disturbance. Consistent with this view, the trend towards a main effect of groups on body PPT disappeared when an ANCOVA with BMI as a Covariate was performed ($F(3,33) = 0.5$, $p > 0.7$). Overall, data suggest ED patients have fairly normal pressure pain threshold over the body.

Figure 7. Mean Pressure Pain Thresholds (Mean ± SD) over the body for Eating Disorder patients and Controls.



3.6.3 Ischemic Pain

Figure 8 shows mean ischemic pain threshold and mean ischemic pain tolerance for each group. Data is expressed in seconds. One participant in the AN-Restrictive Subtype was excluded from the analysis due to missing data. Using Repeated Measure ANOVA, no significant differences were found between the groups on ischemic threshold or ischemic tolerance ($F(3,34)= 1.1$, $p > 0.3$). Figure 9 shows participants ratings of distress and sensitivity following the ischemic pain test. Data is expressed as mean scale scores (0-10), with 0 representing "no distress at all" on the pain distress scale, and "no pain at all" on the sensory pain scale; and 10 representing "very severe distress" on the pain distress scale and "most severe pain possible" on the sensory pain scale. No significant differences were found between the groups on either scale, but as Figure 9 shows, there is a trend for BN patients to be less affected emotionally by pain stimuli than other groups.

These results, when added to the fact that ED patients showed normal overall pain complaints and normal overall pain distress (see section 3.5), suggest that women suffering from EDs have normal pain experiences, that is, their perception of pain and associated affects do not differ from non-ED women.

Figure 8. Ischemic Threshold and Tolerance (Mean ± SD) for Eating Disorder patients and Controls.

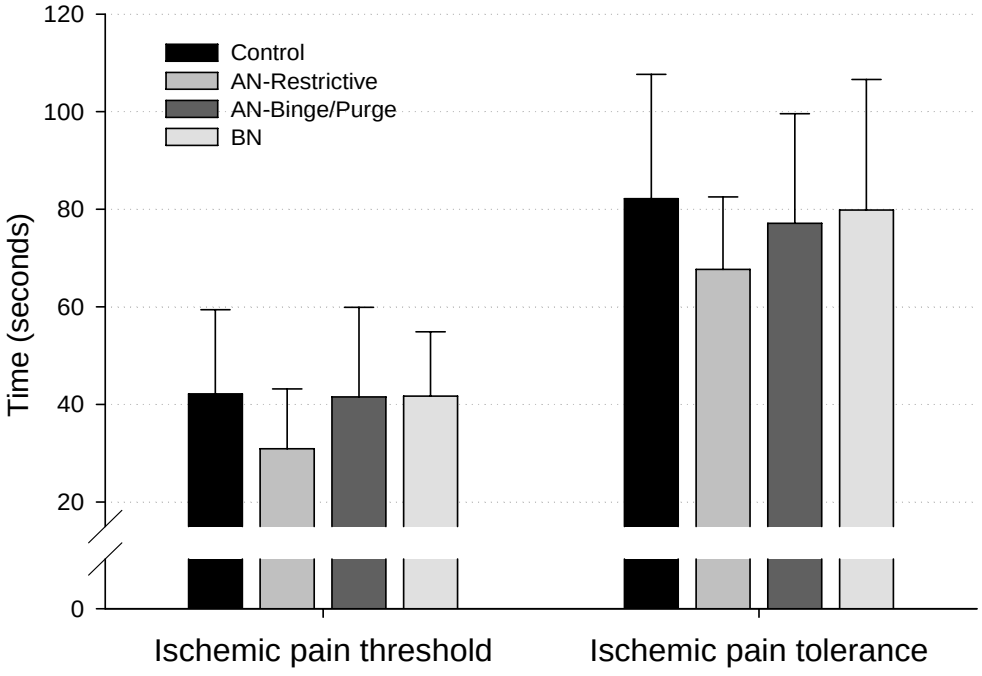
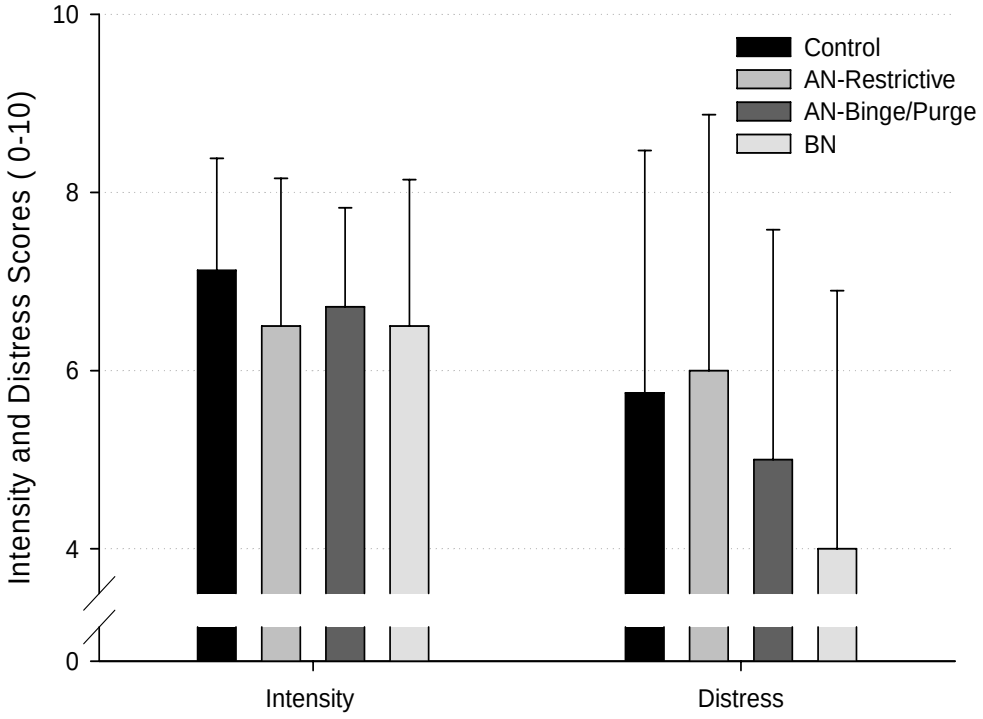


Figure 9. Ratings of Pain Intensity and Pain Distress (Mean ± SD) following the Ischemic Pain Test for Eating Disorder patients and Controls.

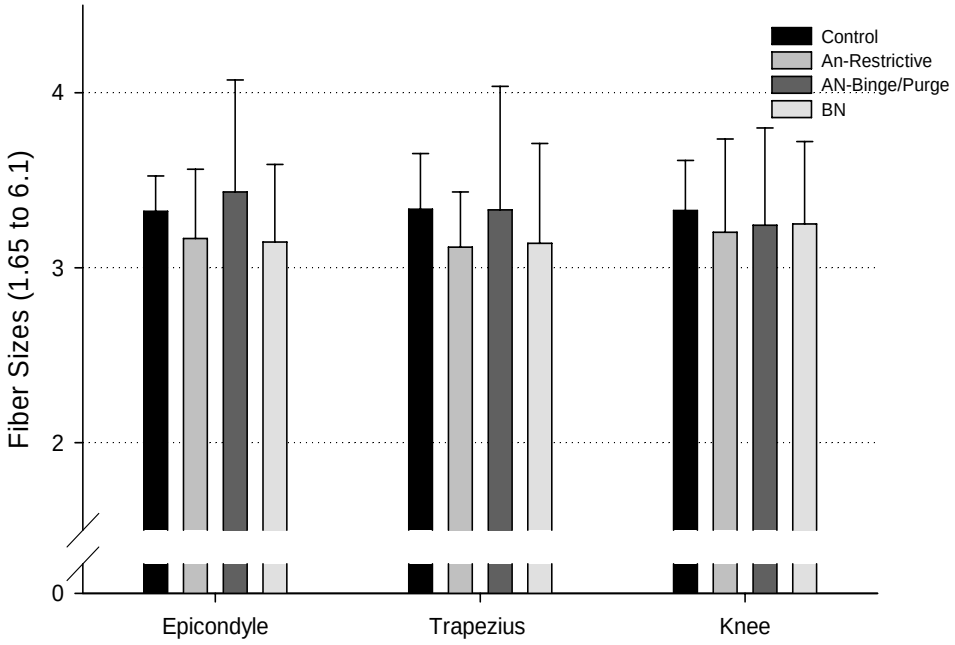


3.7 Somatosensory Measures other than Pain

3.7.1 Punctate Tactile Thresholds

Figure 10 shows mean punctuate tactile threshold for each group. Results are expressed as fiber sizes (were averaged over left and right sides). No significant differences were found between the groups ($F(3,35)=1.1$, $p > 0.3$). These results support the absence of a general disturbance in cutaneous tactile sensitivity in women suffering from EDs.

Figure 10. Punctate Tactile Thresholds (Mean ± SD) for Eating Disorder patients and Controls.

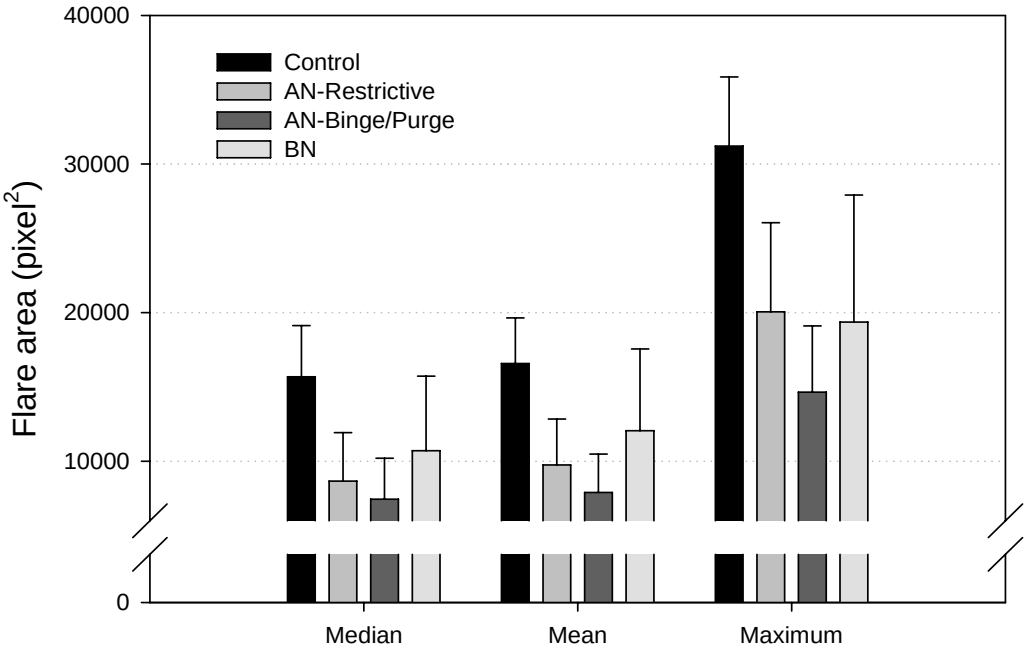


3.7.2 Skin Inflammatory Response

The response to capsaicin was somewhat inconsistent in that the majority of subjects failed to show any response to some of the stimuli[46]. Because the blank responses were frequently in the middle of the series, this suggests problems with adequate skin contact, possibly because the disks of paper used were smaller than those used previously. It is also possible that the skin in our subjects had a higher density of down. Despite these problems, there were measurable responses to most of the stimuli, and to quantify the responses, the median flare size for each subject was computed. This could be considered to be a non-parametric estimate of the ED50 for each subject; using the maximal or mean response yields a very similar pattern. As Figure 11 shows, there was a weak trend for the response to be higher in the control group, and the lowest response was in the AN-binge/purge group ($F= (3,31)= 1.08$, $p > 0.2$). The relationship between the capsaicin response and mood was more informative (see section 3.12).

[46] 4 participants were excluded due to missing data making analyses impossible (i.e. N = 35). Specifically, 2 patients with AN-restrictive, 1 patient with AN-B/P and 1 control were excluded.

Figure 11. Median (Median ± SE), Mean (Mean ±SE) and Maximum (Max ± SE) Responses to Capsaicin for Eating Disorder patients and Controls.



3.8 Autonomic Nervous System Functioning

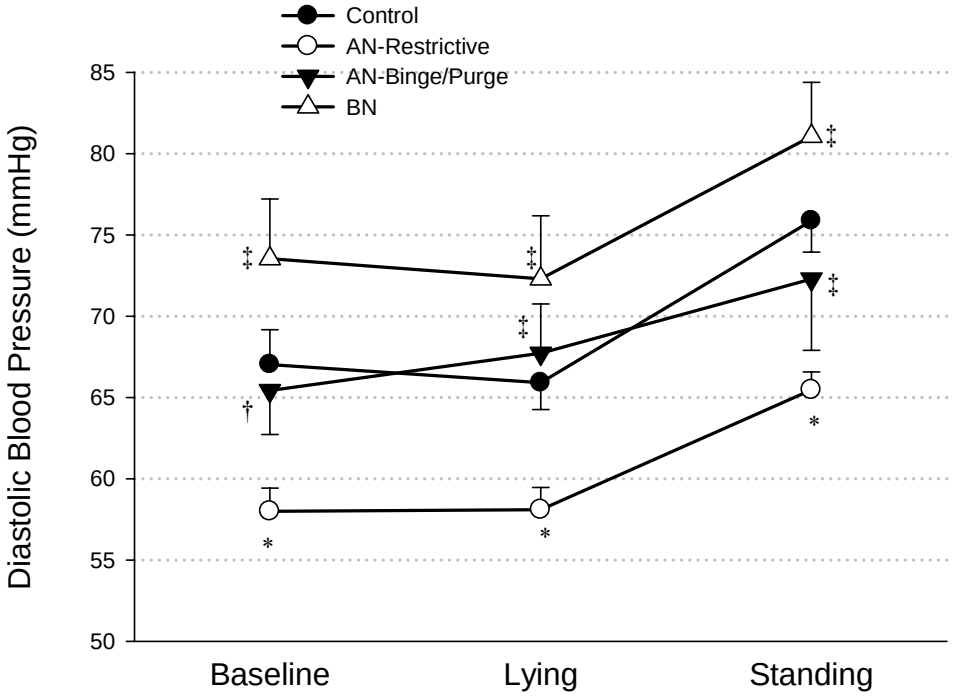
3.8.1 Blood Pressure

Figure 12 and Figure 13 show diastolic and systolic blood pressure (BP) respectively for each group under 3 different conditions; that is, while sitting down for 20 minutes (i.e. baseline condition), laying down for 4 minutes (i.e. resting condition) and standing up for 4 minutes (mild stress condition). Due to missing data, one participant from the AN-restrictive group was excluded from BP analyses. Differences in BP between groups were most prominent for systolic blood pressure during the mild stress condition[47] and least prominent for diastolic blood pressure at baseline and during rest ($F(3,37) \geq 5.6$, $p < 0.01$). BN patients showed the highest BP; while both AN patients groups showed the lowest BP, with the AN patients with Restrictive Subtype having substantially lower BPs than the AN with Binge/Purge Subtype ($p < 0.01$).

ANCOVA with BMIs as a Covariate revealed that, BMIs were significantly related to systolic blood pressure under all conditions[48], and that, after controlling for BMI's, there was still a significant main effect of groups[49] on systolic blood pressure during the mild stress condition (i.e. standing condition in the orthostatic challenge).

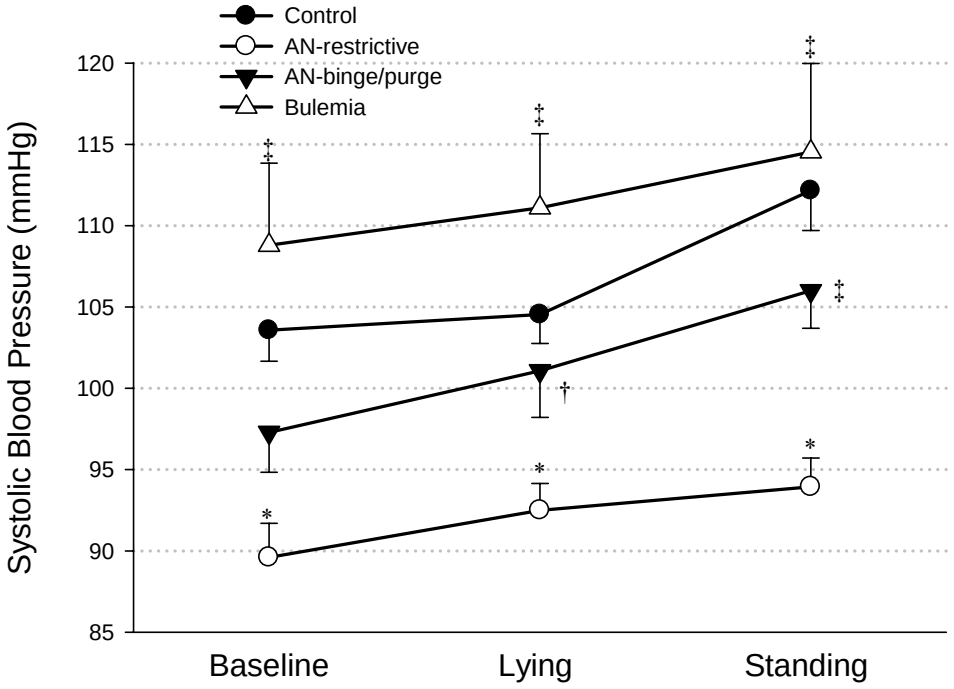
[47] $F = (3,36) = 11.1$, $p < 0.01$
[48] $F(1,37) \geq 4.8$, $p < 0.05$
[49] $F= (3,37) = 3.7$, $p < 0.05$

Figure 12. Mean Diastolic Blood Pressure (Mean ± SE) during Baseline (Baseline), Resting Supi (Lying) and Mild Stress (Standing) for Eating Disorder patients and Controls.



* $p < 0.01$ relative to the Control
† $p < 0.05$; ‡ $p < 0.01$ relative to the AN Restrictive group

Figure 13. Mean Systolic Blood Pressure (Mean ± SE) during Baseline (Baseline), Resting Supi (Lying) and Mild Stress (Standing) for Eating Disorder patients and Controls.

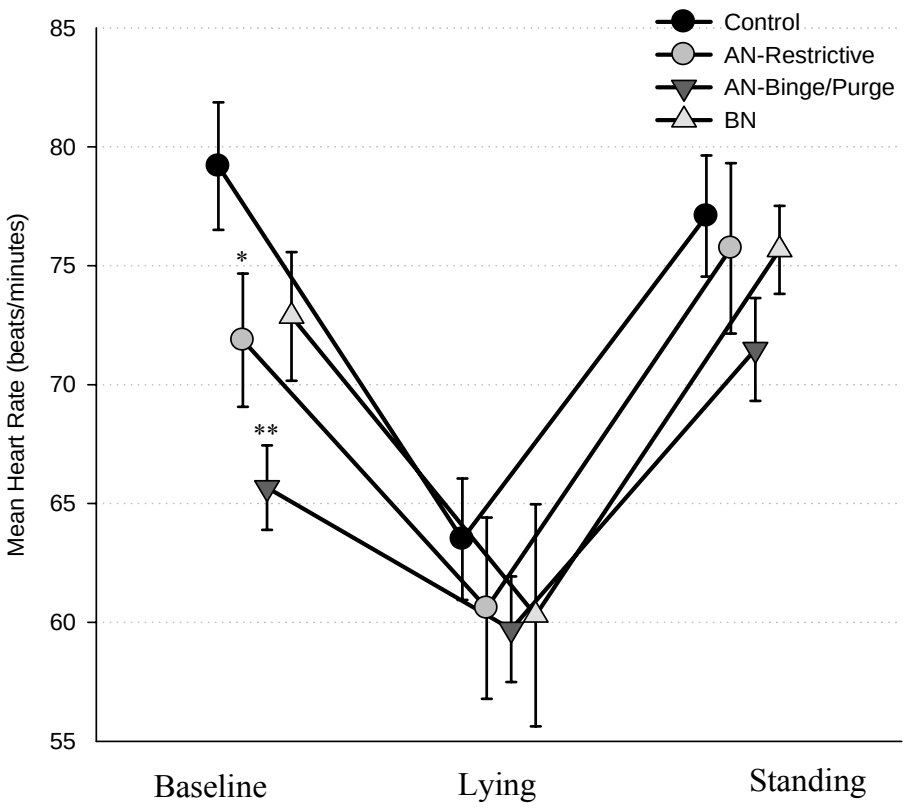


* $p < 0.01$ relative to the Control
† $p < 0.05$; ‡ $p < 0.01$ relative to the AN Restrictive group

3.8.2 Heart Rate Measures

Figure 14 shows mean heart rates (HR) for each group on all 3 conditions (i.e. baseline, resting and mild stress). Due to missing data, one participant from the AN-restrictive group was excluded from HR analyses. ANCOVA with frequency of exercise as a Covariate showed no effect of exercise frequency on HR and did not yield any significant differences between groups for HR. ANOVAs were performed for each condition separately. There was a significant different between groups on HR at baseline ($F(3,37) = 4.0$, $p < 0.05$). Post-hoc comparisons revealed that both AN patients groups had significantly slower HR than controls, with AN patients with Binge/Purge Subtype exhibiting the slowest HR ($p < 0.05$ and $p < 0.01$ for the AN Restrictive and AN Binge/Purge respectively). Curiously, controls showed faster HR at baseline than during the mild stress condition; however, it should be noted that a majority of controls were tested in a location that required them to walk up a hill about 15 minutes before testing began, which could have inflated their heart rate at the time baseline HR was recorded.

Figure 14. Mean Heart Rate (Mean ± SE) during Baseline (Baseline), Resting Supine (Lying) and Mild Stress (Standing) for Eating Disorder patients and Controls.



*p < 0.05, **p < 0.01 relative to the Control

3.8.3 Sympathetic and parasympathetic functions

Figure 15 shows mean Heart Rate Variability (HRV) for each group on all 3 conditions (i.e. baseline, resting and mild stress). HRV was assessed using the root-mean square of the difference of successive R-R intervals[50] (rMSSD index), with higher scores on the rMSSD index indicating higher HRV. (see introduction and methods for an in-dept discussion). Due to gaps and/or gross abnormalities in some of the recordings, certain participants were removed from data analysis of HRV, LF/HF ratio and/or stress responses[51]. Stress-response recordings suffered the most abnormalities and/or gaps, with 11 participants having to be removed; while HRV recordings were the least problematic, with only 3 participants having to be removed. Participants excluded from data analyses were scattered throughout the different groups. Analyses of autonomic function were also performed without removing abnormal recordings. This reduced the variance considerably.

Contrary to expectations, no difference could be found between groups on overall HRV, as well as HRV during specific conditions (i.e. baseline, resting and mild stress). However, it should be noted that AN patients with Restrictive Subtype reliably showed the lowest HRV when compared to the other groups, that is, under all 3 conditions.

Figure 16 illustrates sympatico-vagal balance for each group across all 3 conditions. (i.e. baseline, resting and mild stress). Data is expressed as the ratio of Low Frequency Spectrum (0.04-0.15Hz) to High Frequency Spectrum (0.18-0.4 Hz), with an increased LF/HF ratio representing an increase in sympathetic cardiac control and/or a decrease in parasympathetic control and a decreased LF/HF ratio, the inverse. For a more in-dept discussion of power spectral density, see the introduction. Consistent current knowledge on parasympathetic-sympathetic control during relaxation and during stress, the resting condition was associated with the highest level of parasympathetic control (i.e. lowest LF/HF ratio); and the mild stress condition was associated with the highest level of sympathetic control (i.e. highest LF/HF ratio).

[50] Time elapsed between two consecutive R waves in an electrocardiogram.
[51] LF/HF ratio and Stress responses analyses are discussed in the following sections.

Contrary to expectations, Repeated Measures ANOVA did not reveal any differences between groups on overall sympathetic-parasympathetic balance. One-way ANOVAs were performed to look at group differences for each condition separately (i.e. baseline, resting and mild stress) and revealed a significant difference between groups at baseline ($F(3, 34)= 3.9$, $p < 0.05$). LSD post-hoc comparison showed that AN patients with Binge/Purge Subtype had significantly decreased LF/HF ratio when compared with controls and BN patients ($p < 0.01$ and $p < 0.05$ respectively), which would suggest a general decrease in sympathetic drive or a general increase in parasympathetic drive According to the literature, it is most likely that the decreased LF/HF ratio we observed in AN patients with Binge/Purge Subtype is due to a decreased sympathetic drive. (Kennedy & al., 1989; Nishita & al., 1986).

To assess sympathetically-mediated stress response, differences between parasympathetic and sympathetic balance, BP and HR while standing and resting were computed and analyzed (i.e. Orthostatic challenge, see method). Surprisingly, no differences were found between groups for both HR and sympathetic stress responses. That is, ED patients and controls had a similar stress-response following the orthostatic challenge, as indicated by the normal compensatory increase in HR and normal activation of the sympathetic system observed in all groups. Although not reaching significance, Repeated Measures ANOVA revealed a difference between groups on overall BP (diastolic and systolic) following the orthostatic challenge ($F(3, 33)= 2.6$, $p < 0.07$). ANOVAs were perform on stress-induced variation in Diastolic and Systolic BP separately and revealed a significant difference between groups on Systolic BP ($F(3, 36) = 3.6$, $p < 0.05$). Figure 17 shows variations in systolic blood pressure during the orthostatic challenge. LSD post-hoc comparisons revealed that AN patients with Restrictive Subtype had strikingly lower increments in systolic BP than controls during the orthostatic challenge ($p < 0.01$). That is, AN patients with Restrictive subtype had a slightly reduced stress-response, as indicated by their “less than normal” increase in systolic blood pressure during the mild stress condition. Although not significant, other ED groups also showed smaller reductions in their stress-response in terms of sympatically-mediated increases in systolic blood pressure during the orthostatic challenge.

Overall, data suggest that ED patients under treatment, even though they still suffer from high levels of ED symptomatologies, have relatively normal autonomic function. Autonomic function was not, however, completely normal, with the different ED symptomatologies being associated with their own specific disturbances, some of the disturbances being opposite to one another (e.g. elevated BP in BN patients and decrease BP in AN patients with Restrictive Subtype). By and large, results shows that BN patients are similar to controls on their autonomic functions, while AN patients have lower HR and BP, indices of the effect of starvation. Finally, results suggest that both AN patients groups suffer small disturbances in their autonomic function; the AN patients with Binge/Purge Subtype showing a minor sympathico-vagal imbalance, but a fairly normal stress response; and the AN patients with Restrictive Subtype showing a slightly reduced stress-response, but a fairly normal sympatico-vagal balance.

Figure 15. Mean Heart Rate Variabitlity (Mean ± SE) during Baseline (Baseline), Resting Supine (Lying) and Mild Stress (Standing) for Eating Disorder patients and Controls.

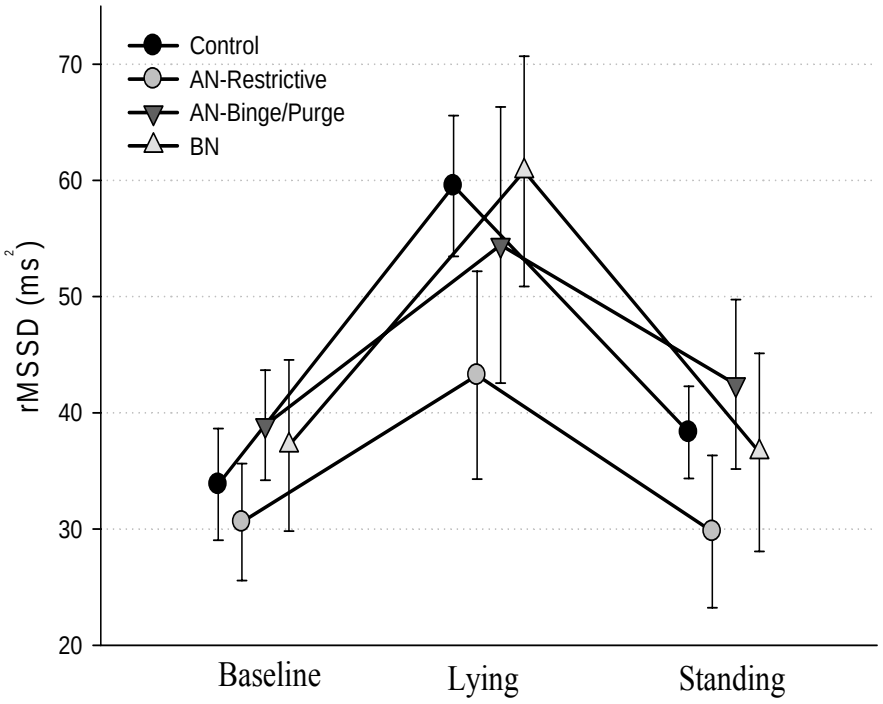
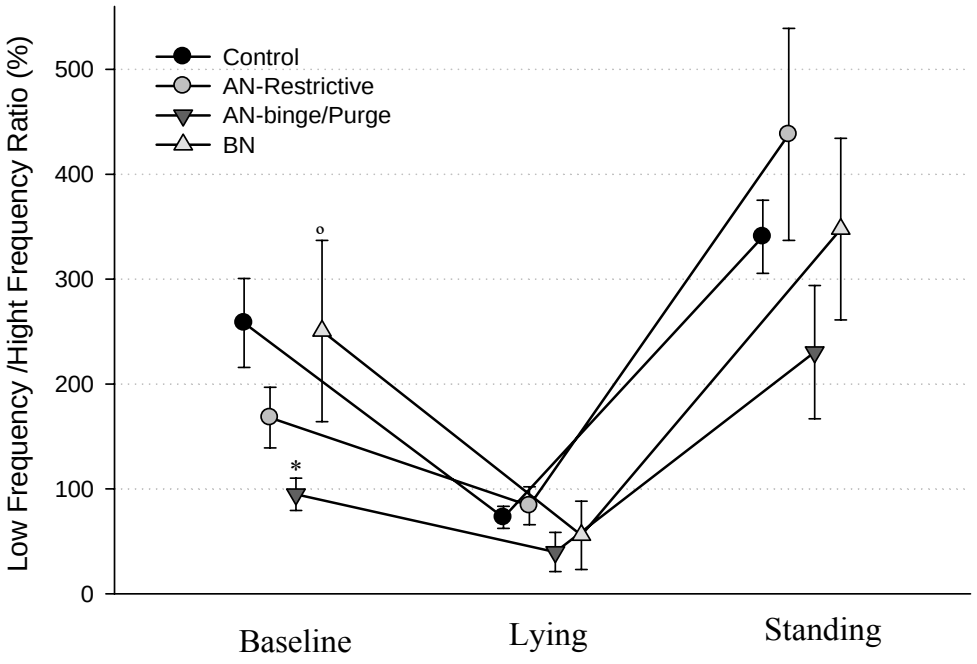
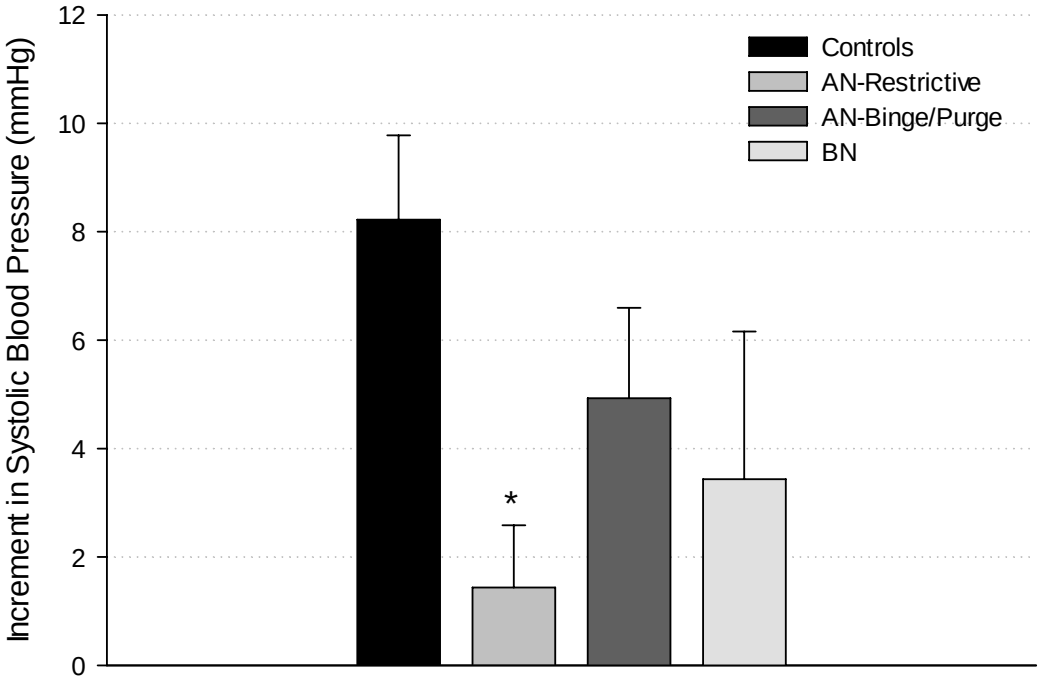


Figure 16. Sympathetic-Vagal Balance presented as Mean Low Frequency to High Frequency spectrum ratio (Mean ± SE) during Baseline (Baseline), Resting Supine (Lying) and Mild Stress (Standing) for Eating Disorder patients and Controls.



* $p < 0.01$ relative to the Control
º $p < 0.05$ relative to the AN-Binge/Purge Subtype

Figure 17. Sympathetically-mediated increments (Mean ± SE) in Systolic Blood Pressure during a Mild Stress Condition (Orthostatic Challenge) for Eating Disorder patients and Controls.



* $p < 0.01$ relative to the Control

3.9 Medication

A general classification of medication intake for each group is presented in Table 3. Since none of the controls were taking any psychotropic medications, they were excluded from the following analyses. Repeated Measures ANOVA showed that there was no significant difference on any of the General Health or Psychological Indices between patients taking psychotropic medication[52] and medication-free patients. These results are theorically important since they suggests that, even on the measures that are expected to be the most affected by psychotropic medications, that is, psychological health and functioning, ED patients taking medication and medication-free ED patients did not differ.

In order to rule out confounding effects of medication on somatosensory measures and pain measures, statistical analyses were also performed to test for differences between patients taking medication and medication-free patients. Effects of specific categories of medication (i.e. serotonergic, major tranquilizers and miscellaneous) were also tested. Repeated Measures ANOVA revealed a significant difference between ED patients taking serotonergic (5-HT) medication and ED patients not taking serotenergic medication[53] on their punctuate tactile threshold (PTT). Specifically, ED patients taking 5-HT medication had lower PPT, that is, higher sensitivity to light touch, than ED patients not taking 5-HT medication ($F(1, 21) = 4.8$, $p < 0.05$).

Importantly, ED groups did not differ from each other or the controls on any of the other sensory functions, including pain measures and thus, the difference between ED patients taking serotonergic medication and ED patients not taking serotonergic medication on their PTT, although warranting further investigation, does not imply that medication played a confounding role in the present study. Also in support of medication not playing a key role in determining somatosensory sensitivity, particularly pain, is the fact that no meaningful differences were found between patients taking medication[54] and

[52] Psychotropic medication refers to serotonergic medication, major tranquilizers and miscellaneous medications. See Table 3 for a list of the specific medications included in each category of medications.
[53] This group includes patients taking psychotropic medications other than serotenergic medication as well as medication-free patients.
[54] Medication refers, here, to any psychotropic medication; as well as specific classes of psychotropic medication (i.e. serotonergic, major tranquilizers and miscellaneous)

medication-free patients on any of the pain measures or any of the somatosensory measures, besides sensitivity to light touch (i.e. PTT). Determining the link between PPT and serotonergic medication is out of the scope of this study, but we believe that our results justify the need for future research to explore further the relationship between serotenergic medication and general sensory function.

3.10 Relationship between ED Symptomatology and Somatosensory Sensitivity

To explore the relationship between ED symptomatology and somatosensory sensitivity, Pearson's correlations were performed between specific ED symptoms/characteristics[55] and sensory measures[56] Unless specifically relating to ED behaviors (i.e. vomiting, laxative abuse, fasting for 8 hours or more, etc.), all participants, that is both controls and patients, were included in these analyses, including correlations with BMI.

First, BMIs were found to be positively associated with overall pressure pain threshold over the body ($r = 0.40$, $p < 0.05$). As mentioned above (see section 3.6.1), this is to be expected since individuals which have more lean muscles and/or fat tissue have higher BMIs, and the amount of pressure required to elicit pain is greater when there are more tissues to compress. Unsurprisingly, BMIs also correlated positively with BP, particularly with systolic BP ($r \geq 0.47$, $p < 0.01$). Finally, BMIs also correlated with Pain Pressure Threshold (PPT) on the hands ($r = 0.34$, $p < 0.05$).

In addition to correlating with BMIs, Hand PPT was positively related to frequency of exercise and feeling of fatness in the month prior to testing ($r = 0.44$, $p < 0.05$; and $r = 0.42$, $p < 0.05$ respectively). Also, there was a trend for fear of weight gain in the month prior to be positively associated with hand PPT ($r = 0.41$, $p > 0.06$). Differences in hand PPT were related to BMIs and, more strongly, to exercise frequency, but the proportion of variance explained was low[57]. Also, the fact that fear of weight gain

[55] ED symptoms/characteristics include, amongst other things, BMI, extreme exercise, laxative use, vomiting, bulimic episodes, fear of weight gain, feeling of fatness and importance of shape and weight.
[56] Sensory measures include indices of autonomic function, skin reactivity, pain sensitivity pain sensitivity (i.e. pressure pain threshold on the hand, pressure pain threshold over the body and ischemic pain threshold and tolerance) and aches and pains.
[57] $r^2 = 0.09$ for BMI and $r^2 = 0.1$ for Exercice Frequency

and feeling of fatness in the month prior to testing also correlated with hand PTT indicates that overall severity of ED patients symptomatology, rather than specific behaviors, relate to the elevated pressure pain thresholds observed in some ED patients.

Although no significant differences were found between controls and ED patients on their Ischemic Threshold and Tolerance, Pearson's correlation revealed strong positive correlations between the frequency of exercise in the month prior to testing and the Ischemic Thresholds as well as the Ischemic Tolerance ($r = 0.52$, $p < 0.05$; and $r = 0.70$, $p < 0.01$, respectively). These results are likely to reflect differences in cardiovascular capacity and/or efficiency between sedentary and active women.

Contrary to what we hypothesized, none of the ED symptomatologies besides BMIs (see above) correlated with any of the indices of autonomic functions. The exploration of ED symptomatology and aches and pains was more interesting. First, frequency of painful constipation, tension headache and, to a lesser extent, migraines were all positively correlated with frequency of vomiting in the month prior to testing ($r \geq 0.346$, $p < 0.05$) . Migraines also correlated with laxative abuse and exercise frequency in the month prior to testing ($r \geq 0.35$, $p < 0.05$). Since vomiting, laxative abuse and extreme exercise are all considered to be stressful to the body, our data supports a relation between stress and increased frequency of migraines.

Although painful constipation did not correlated with a specific ED behavior, it was found to negatively correlate with the number of weeks without compensatory behavior ($r = 0.43$, $p < 0.05$) (i.e. vomiting, laxative, fasting, etc.), suggesting again that the aches and pains experienced by ED patients are directly related to their behaviors rather than being a reflection of a general disturbance in pain sensitivity.

Also supporting the improbability of a general disturbance in ED patients pain experience is the fact that; while specific pains were found to positively correlate with specific ED behaviors, total pain complaints and pain distress did not related to ED symptomatologies. In light of these facts, data suggest that by in large, women suffering form EDs have normal pain experiences.

3.11 Relationship between Autonomic Function and Somatosensory Sensitivity

With the aim of examining relationships between autonomic function and somatosensory sensitivity, Pearson's correlations were performed between indices of autonomic function[58] and sensory measures[59]. Participants, controls and patients, were all included in these analyses, but there were some scattered missing data.

Blood pressure, in particular systolic BP, correlated positively with all measures of capsaicin reactivity, that is, with maximum, mean and median flare responses ($r \geq 0.44$, $p < 0.01$). It should be noted that elevation in systolic blood pressure does not entail elevated blood pressure in the present study, Indeed, since the majority of the control group is comprised of young healthy women, the highest systolic BPs recorded were still in the low-normal range (see Figure 13). These results suggest autonomic function and inflammatory response are related.

Although BP did not significantly correlate with any of the pain sensitivity measures; because of the link between high blood pressure and elevated pain thresholds (see introduction); and the fact that BN patients showed both elevated BP and elevated pressure pain threshold on the hand, the relationship between BP and pressure pain thresholds on the hand was also tested. ANCOVA showed a small effect of systolic BP on hand PPT that did not reach significance ($p > 0.09$) and that could not account for the elevated hand PPT observed in BN patients (see section 3.6.1). eartHeart rate

While data suggest that the elevated pressure pain on the hand observed in women with BN are not explained by disturbances in the autonomic nervous system, they clearly show the existence of a link between the autonomic system, inflammatory responses and general sensitivity, including pain sensitivity.

[58] Autonomic measures include blood pressure, heart rate, heart rate variability, sympatico-vagal balance and indices of stress-response.
[59] Sensory measures include indices of skin reactivity, pain sensitivity (i.e. pressure pain threshold on the hand, pressure pain threshold over the body and ischemic pain threshold and tolerance) and aches and pains.

3.12 Relationship between Psychological Measures and Somatosensory Measures

The relationship between general health (physical and psychological) and somatosensory sensitivity was examined using Pearson correlations. Specifically, correlations between 1) General Physical Health (GPH) and General Mental Heath (GMH) as measured by the SF-36; Psychological distress (GSI) and Symptom Severity (PSDI) as measured by the SCL-90-R; Depression and Anxiety as measured by the HADS; overall pain complaints; and 2) somatosensory measures[60] were performed. All participants, controls and patients, were included in the following analyses, but there were some scattered missing data.

First, the relationship between pain measures and general health was explored. A moderate positive correlation was found between General Mental Health ($r = 0.43$, $p < 0.01$) and pressure pain threshold on the hand (hand PPT). These results are likely to reflect the fact that AN patients groups exhibited the lowest hand PPTs as well as the lowest General Mental Health Scores. (see Figure 6 and Figure 1, respectively). Although not significant, there was also a trend towards anxiety scores on the HADS to correlate positively with pressure pain threshold on the hand ($r = 0.31$, $p > 0.06$). While ischemic tolerance did not correlate with any measures of psychological health, ischemic threshold was found to be moderately positively related to psychological distress ($r = 0.37$, $p < 0.05$). Thus, despite the inconsistencies, considered as a whole; results suggest a relation between mental health and pain sensitivity.

Results on autonomically-mediated stress-response and indices of psychological functioning are more revealing. First, higher general mental health strongly correlated with larger stress-response[61] ($r = 0.540$, $p < 0.01$). Similarly, reduced stress-response correlated with increased severity of overall psychopathologies[62] ($r = -0.36$, $p < 0.05$) , as

[60] Somatosensory measures include indices of skin reactivity, pain sensitivity (i.e. pressure pain threshold on the hand, pressure pain threshold over the body and ischemic pain threshold and tolerance) and aches and pains.
[61] as indicated by increases in systolic BP during the othostatic challenge (see section 2.2.11 on autonomic function in the Introduction)
[62] as measured by the Symptom Severity Index (PSDI) of the SCL-90-R

well as increased depressive symptomatology[63] (r = - 0.52, p < 0.01) and increased anxiety symptomatology[64] (r = -0.327, p < 0.05).

Exploration of aches and pains and psychological functioning yielded some interesting results as well. First, Psychological distress (GSI) and Symptom Severity (PSDI) were both moderately positively correlated with overall aches and pains (r = 0.47, p < 0.01 and r = 0.43, p < 0.01, respectively) Depression and anxiety symptoms were also both related to total frequency of pain complaints. (r = 0.4, p < 0.01 and r = 0.32, p < 0.05 respectively)

Overall, the data on autonomic function, general health and psychological functioning indicate a relationship between low mood, anxiety and a reduced capacity to respond to stress, as well as a disturbed pain experience, as indicated by a higher frequency of pain complaints. In light of these facts, we argue that the comorbidity of anxiety and depression with EDs is not only meaningful, but is also likely to underlie an important proportion of the autonomic, endocrine and general sensitivity disturbances observed in some women suffering from eating disorders.

In order to explore further the relationship between mood, in particular anxiety and depression, and somatosensory sensitivity, participants were divided into 4 categories using clinically established cut-off points on the depression and anxiety scales of the HADS (See Olsson, Mykletun and Dahl; 2005). Specifically, participants were divided into groups according to the severity of their symptoms: Normal, mild, moderate and severe. Table 4 shows the proportion of individuals in each group according to their depression and anxiety classifications. Since there were no severely depressed individuals in the controls or any of the ED patients groups, the severely depressed category was removed from the Table.

The 4 anxiety and the 3 depression groups did not differ from each other on any of the pain measures. Data on the autonomic system and its relationship with depression and anxiety are more revealing. First, ANOVA showed a significant difference between

[63] The stress-response refers, in this case, to an increases in the low-frequency spectrum during the orthostatic challenge in this case (see discussion on autonomic function in the introduction)
[64] The stress-response refers, in this case, to an increase in systolic BP (see discussion on autonomic function in the introduction)

depression groups for heart rate at baseline[65] ($F(2,37)= 4.4$, $p < 0.05$). Specifically, moderately depressed individuals had significantly slower heart rate than individuals with normal mood ($p < 0.01$). Most importantly, there was also a meaningful difference between the different depression groups and the stress-response during the orthostatic challenge ($F(3,27) = 4.0$, $p < 0.05$). As Figure 18 shows, sympathetically driven stress-response was reduced[66] in both mildly and moderately depressed individuals when compared to individual with normal mood, but only the difference between the mildly depressed and normal was significant ($p < 0.05$).

Figure 19 shows total frequency of pain complaints according to the different depression groups. ANOVA revealed a significant difference between the different depression groups on total frequency of pain complaints ($F(2,38) = 3.3$, $p < 0.05$). LSD post-hoc comparison revealed that moderately depressed individuals reported significantly more aches and pains than individuals classified as normal ($p < 0.05$).

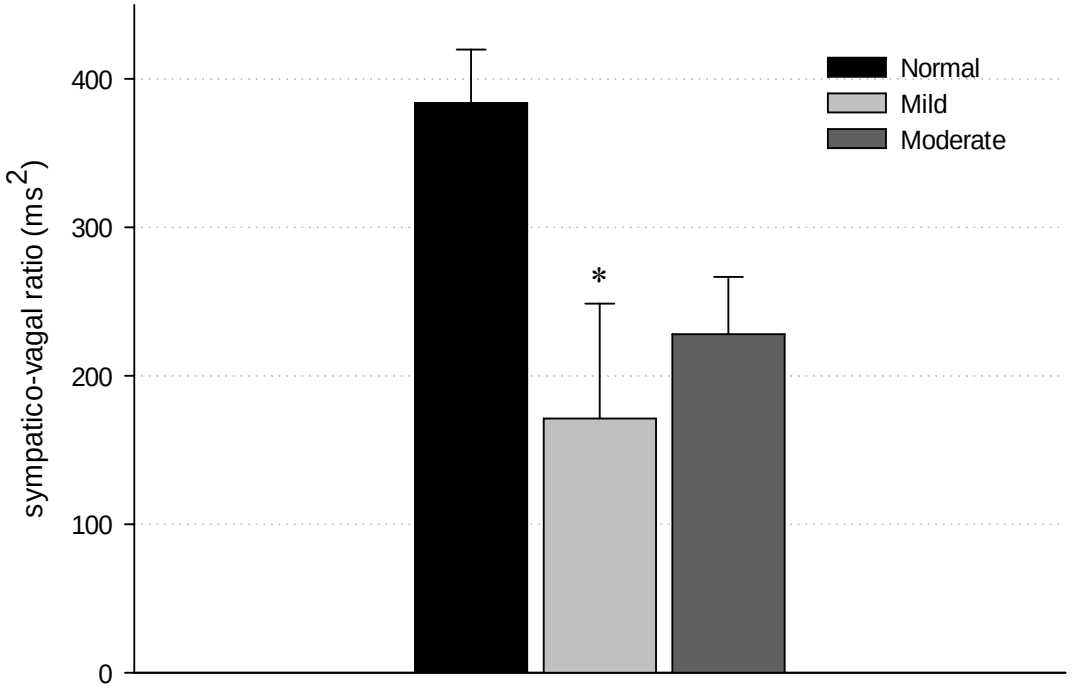
It is also noteworthy that severely anxious individuals reported more pains than all other anxiety groups and that this difference almost reached significance ($F(2,38)= 2.8$, $p > 0.06$). As Figure 20 shows, severely anxious individuals reported roughly twice as many aches and pains[67] than individuals classified as normal, mildly and moderately anxious. Results suggests that depression and, to a lesser extent, anxiety relate to aches and pains and might play a role in the development and/or maintenance of pain-related conditions.

[65] Baseline refers to HR recordings while sitting down
[66] as indicated by a lower sympatico-vagal ratio when standing up (Mild stress condition)
[67] as indicated by the total frequency of aches and pains for all 19 categories of pain

Table 4. Distribution of HADS clinical depression and anxiety in Eating Disorder patients and Controls.

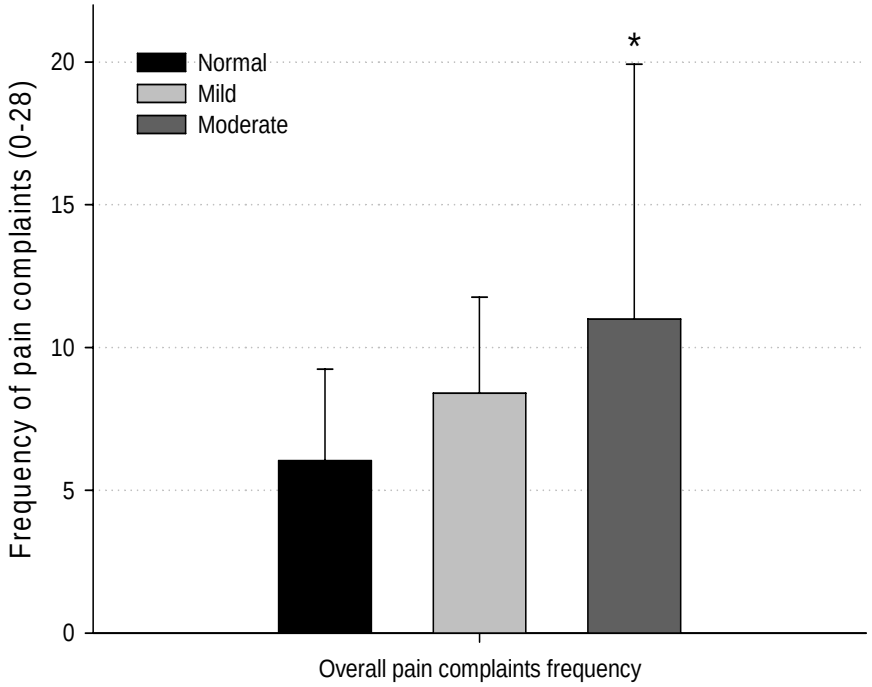
Participant's Group; Proportion				
DEPRESSION				
Severity of Symptoms	**Control**	**AN patients: Restrictive Subtype**	**AN patients: Binge/Purge Subtype**	**BN patients**
Normal	**15**/16	**7**/10	**1**/7	**4**/6
Mild	**1**/16	**1**/10	**2**/7	**1**/6
Moderate	**0**/16	**2**/10	**4**/7	**1**/6
ANXIETY				
Severity of Symptoms	**Control**	**AN patients: Restrictive Subtype**	**AN patients: Binge/Purge Subtype**	**BN patients**
Normal	**8**/16	**3**/10	**0**/7	**1**/6
Mild	**4**/16	**1**/10	**0**/7	**2**/6
Moderate	**4**/16	**3**/10	**4**/7	**3**/6
Severe	**0**/16	**3**/10	**3**/7	**0**/6

Figure 18. Mean Sympatico-vagal ratio (Mean ± SE) during a Mild Stress Condition (Orthostatic Challenge) for Eating Disorder patients and Controls.



* $p < 0.01$ relative to Normal

Figure 19. Overall pain complaints (Total ± SD) according to the severity of depression symptomatology



* p < 0.05 relative to the Control

CHAPTER 4

DISCUSSION

The primary goal of the present study was to better describe the relationship between eating disorders and psychological, autonomic and somatosensory functions, in particular pain thresholds and tolerance. Contrary to our expectations, overall, ED patients in treatment, although still exhibiting high level of ED symptomatologies and suffering marked psychological impairments, had a relatively normal physical health, somatosensory sensitivity including pain sensitivity and autonomic function.

Although differing from prior hypotheses, our findings are not necessarily inconsistent with the literature on EDs, since previous studies have suggested that the majority of the physiologic alterations associated with starvation, return to normal after AN patients attain a normal weight (Nishita &al., 1986; Rechlin & al., 1998). In the present study, even though 6/17 and 14/17 AN patients were still severely underweight (i.e. BMI < 16) and underweight (BMI < 18) respectively, our findings are similar to theirs. Our findings suggest that, even though ED patients might not be completely recovered and might still show signs of severe starvation, once a positive energy balance is established, they do not suffer persisting damage to their general health or autonomic functions. In other words, once ED patients show a noticeable decrease in compensatory behaviours[68] and/or cease to loose weight, their homeostatic systems return to normal.

Taking into account the general assumption that ED patients have impaired physical health, it is surprising that the large majority of ED patients rated their physical health as good to very good (Figure 1). Moreover, BN patients all reported a physical functioning at the "100%" level which is actually higher than what is expected from non-ED populations according to the SF-36 normative data on 12-24 years old Canadian women (90.9± 14.8)[69]. Disturbed physical health perceptions and/or refusal to acknowledge physical impairments is unlikely to be responsible for these results since the

[68] These include, amongst other, vomiting, laxative abuse and extreme exercise.
[69] Mean ± SD; See Hopman et al. (2000)

evaluation of physical health by the SF-36 general health survey is based on real limitations in physical activities, such as difficulty walking or climbing stairs. Interestingly, ED patients, in particular AN patients, had significantly lower scores on Role-Physical and, to a lesser extent, on Vitality when compared to controls (Figure 1), which suggests that the maintenance of such high physical health is costly. In other words, ED patients are able to maintain good physical functioning, but they have to spend a great deal of energy doing so and it is at the sacrifice of other areas of their life.

As is well documented, ED patients showed marked impairments in their general mental health, with the AN patients with Binge/Purge Subtype being, by far, the most impaired psychologically and emotionally of all ED patient groups (Figure 1-4; Results section 3.2 to 3.4). These findings corroborate the conclusions from Herzog and his colleagues (1999) who, after comparing Binge/Purging AN patients with Restrictive AN patients concluded that the Binge/Purging Suptype was associated with a worst prognosis.

Interestingly, the exploration of patients characteristics revealed that both Binge/Purge disorders, that is, AN patients with Binge/Purge Subtype and BN patients shared more similarities in their day-to-day non eating-related behaviors, such as vitamine intake and pain medication intake than both AN patient Subtypes (see Table 2). These findings suggest that Binge/Purge disorders (i.e BN and AN-B/P) might actually be more analogous to one another, at least in their psychological profiles, than both AN subtypes (i.e. AN-R and AN-B/P). The investigation of Personality Disorders in ED patients has also yielded some evidence for the presence of key differences between Restrictive and Binge/Purging disorders (Steiger & Bruce, 2003).

Exploration of pain sensitivity revealed an elevated pressure pain threshold (PPT) on the hand of patients with BN that correlated positively with BMI, Exercise and Feeling of fatness. Prior findings of hypervagal activity in women with BN, as well as correlation between vomiting and PPT on the hand has led some researchers to believe that stimulation of the vagus nerve was responsible for the elevated PPT observed in women with BN. (Faris et al., 1998; Papezova et al., 2005) Our findings, however, do not support this view since vagal activity did not correlate with pain thresholds on any of the pain measures. Additional evidence against the involvement of the vagus nerve is the fact that

BN patients did not suffer from any sympatico-vagal disturbance (Figure 16) and yet, still showed elevated pain thresholds on the hand (Figure 6). These results are consistent with the study by Raymond et al. (1999a), where the number and frequency of binge-eating/vomiting episodes did not correlate with pain threshold. Since ED patients did not differ from Control on other measures of pain sensitivity (i.e. PPT over the body, ischemic pain threshold and tolerance) and also showed normal cutaneous sensitivity (i.e. punctate tactile thresholds), our findings indicate that the elevated pain thresholds observed in some ED patients are not the expression of a general disturbance in somatosensory sensitivity or in overall pain sensitivity. One could argue that the small sample size is responsible for the lack of significant differences between ED patients and controls on the pain measures, however, the absence of any trends toward elevated pain threshold or tolerance in any of the pain measures[70], except for the PPT on the hand being elevated in BN patients, renders this unlikely. Also in support of a normal pain sensitivity in ED patients in treatment is the fact that the ED patients reported normal pain experiences, that is, their overall pain complaints as well as their perception of pain and associated effects did not differ from non-ED women.

Another aim of the present study was to describe autonomic function and its relation to physiological and somatosensory function. Overall, data suggest that ED patients under treatment, even though they still suffer from high levels of ED symptomatologies, have relatively normal autonomic function. That is, measures of blood pressure, heart rate, heart rate variability, sympatico-vagal balance and sympathetically-driven stress-response in ED patients were generally similar to controls. Autonomic function was not, however, completely normal, with the different ED symptomatologies being associated with their own specific disturbances, some of the disturbances being opposite to one another (e.g. elevated BP in BN patients and decreased BP in AN patients with Restrictive Subtype). By and large, results show that BN patients are similar to controls in respect to their autonomic function, while AN patients have lower HR and BP, indices of the effects of starvation. Finally, the results suggest that the AN patient groups suffer small disturbances in their autonomic function; the AN patients with Binge/Purge

[70] See section 3.6. It should be noted that a small trend towards elevated PPT over the body was observed in BN patients, but that trend was accounted for by differences in BMIs (see section 3.6.2).

Subtype showing a minor sympathico-vagal imbalance, but a fairly normal stress response; and the AN patients with Restrictive Subtype showing a slightly reduced stress-response, but a fairly normal sympatico-vagal balance. These results are, by and large, consistent with previous findings of reduced sympathetic cardiac control in AN patients (Recklin et al., 1998)

Most importantly, our findings on autonomic function, general health and psychological functioning indicate a relationship across both patients and controls between low mood, anxiety and a reduced capacity to respond to stress, as well as a disturbed pain experience, as indicated by a higher frequency of overall pain complaints (Figure 19 and 20, respectively). The importance of a relationship between affect and autonomic functioning is not a trivial one as our results also show a link between the inflammatory response (as indicated by capsaicin skin reactivity) and the autonomic nervous system[71] (see section 3.11), confirming again the close relationship between the different homeostatic systems.

Also, since there was a trend for women suffering from BN to be less affected emotionally by pain stimuli than other groups (Figure 9); and since BN patients also showed elevated PPT on the hand, we suggest that blunted affect could be responsible for the abnormalities in pain sensitivity observed in some women with EDs. Consistent with this view, De Zwaan and colleagues (1996a;1996b) found that depression scores modulated pressure pain thresholds on the hands for both controls and ED patients. In light of these facts, we believe that our findings justify a focus on the emotional component of pain rather than the sensory one in future research on EDs and pain sensitivity. Furthermore, we suggest that disturbances in affect, particularly anxiety and depression, determine to a large extent the specific autonomic and somatosensory disturbances that women with and without EDs might have. Moreover, our findings suggest that the profile of autonomic and somatosensory disturbances exhibited by a specific ED patient is likely to reflect the association between a particular subtype (i.e. BN, AN-R or AN-B/P) and specific comorbid psychopathologies.

Limitations to the present study include small sample size and medication intake in the patients group. Variations in treatment and ED symptom severity within the patient

[71] See section 3.11

groups might also be seen as a limitation, however, it also implies that our sample is much more representative of ED patients population than the samples of studies that have selected untreated and "pure" cases of AN-R, AN-B/P or BN. Also, although sample size was small, results on the different sensory measures were by in large, consistent with each other and prior data, leading us to believe that, even though one should be careful in making strong claims, our results could be replicated in studies with larger sample. Unequal group sizes weaken the power of ANOVA, so that the positive findings are not due to this problem, although the negative findings for group differences could result from the inequalities. Although there was some inequality of variances, this was within the range where transformations or nonparametric analyses, as appropriate, would not be recommended. Another possible limitation concerns the recruitment of controls. Due to ethical requirements, the nature of the study (i.e. pain sensitivity in eating disorders) had to be included in the advertisement for controls. Thus, it is possible that the recruitment of controls was biased towards women that are interested in EDs for personal reasons, such as having a sister or a friend who suffers from an ED. This might have affected the "normality" of our control sample, since women who are interested in eating disorders might differ from women not concerned by ED.

Finally, by exploring the relationship between EDs and neurobiological abnormalities, this study has revealed a pattern across patients and controls for Depression and Anxiety to be tied with abnormalities in autonomic function and the inflammatory response to capsaisin, and possibly abnormalities in pain sensitivity as well. We believe that the link between the different homeostatic systems and comorbid psychopathologies has important theorical and clinical implications, since it validates the importance of acknowledging both the psychological and the physiological disturbances when describing clinical and sub-clinical psychiatric disorders. This also justifies the need for future research to explore further the relationship between psychopathologies, in particular depression and anxiety, and neurobiological abnormalities with the aim of increasing our understanding of the pathophysiology of psychiatric disorders. The description of psychiatric syndromes in terms of neurobiological abnormalities, including abnormalities of pain perception, may also be a useful addendum to the traditional classification, which is based solely on psychopathological features.

CHAPTER 5

CONCLUSIONS

The primary goal of the present study was to better describe the relationship between eating disorders and psychological, autonomic and somatosensory functions, in particular pain thresholds and tolerance. Although pressure pain threshold on the hand was elevated in women suffering from BN, our results does not support the presence of a general disturbance in pain sensitivity or sensory function in ED patients since other measures of somatosensory function, including pain sensitivity, were normal. Contrary to our expectations, ED patients reported relatively normal physical health, somatosensory and autonomic functions. The lack of major disturbances in these systems suggests that, although ED patients undergo severe starvation and/or cause extreme stresses to their body by regularly engaging in compensatory behaviours, they do not suffer persisting damage to their general health or autonomic functions once a positive energy balance is established. That is, once ED patients show a noticeable decrease in compensatory behaviours and/or cease to loose weight, their homeostatic systems return to normal.

Across ED patients and controls, depression and anxiety were both associated with a reduced capacity to respond to stress, as well as a disturbed pain experience, as indicated by a higher frequency of pain complaints. This underlines the importance of exploring the psychological as well as the physiological abnormalities associated with psychiatric disorders, in both clinical and sub-clinical populations, in order to achieve a real understanding of the pathophysiology of psychiatric disorders. Our findings also confirm the importance of treating and assessing comorbid psychopathologies in ED patients, and suggest that therapists ought to consider personality and/or mood impairments that might have preceded the ED.

Finally, there were significant heterogeneities in terms of general health, psychological functioning, somatosensory and autonomic functions within ED subtypes. This has important clinical significance since it implies that, even within subtypes, patients differ in terms of their physical and mental health. Certain authors, have, indeed argued that

there are various clusters of symptomatologies within "binge/purger" subtypes[72] and that, each of these clusters reflect different etiologies. (Steiger, Bruce & Israël, 2003; Vitousek & Manke; 1994). Consistent with this view, our results support the presence of different neurobiological profiles within ED subtypes.

[72] See Steiger & Bruce, 2004 for a description of the different personality clusters within ED subtypes.

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Appendix 1

Participant ID _____

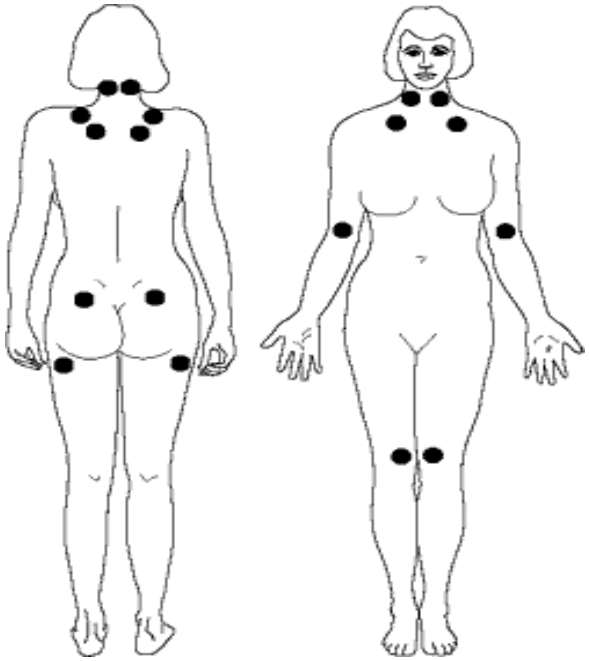
Pressure Pain Thresholds (Hands)

	Threshold (g)
1st finger	
2nd finger	
3rd finger	
4th finger	
5th finger	

Appendix 2

Pressure Pain Thresholds (Body) Participant ID _____

Site	R	L
occiput		
low cervical area		
trapezius		
supraspinatus		
second rib		
lateral epicondyle		
gluteal		
greater trochanter		
knee		



Location of the points at which pressure pain were measured

Appendix 3

Punctate Tactile Thresholds

Participant ID _____

trial #																			
Forearm	R								■					■			■		
	L		■						■		■					■			
Trap.	R			■							■			■					■
	L						■					■			■				■
Knee	R								■					■			■		
	L		■		■							■				■		■	

Comments:

Appendix 4

Participant ID: _____

Ischemic Pain Threshold

Strength

- Maximum Grip Strength (lb): _____

Pain

- Threshold (sec): _____

- Tolerance (sec): _____

Appendix 5

Ischemic Pain Ratings Participant ID _____

On the “0" to “10" scale below, how intense was the pain at the time you withdrew your hand?

0 ---------- 1 ---------- 2 ---------- 3 ---------- 4 ---------- 5 --------- 6 ---------- 7 --------- 8 ---------- 9 ---------- 10

No pain at all *Most severe pain possible*

On the “0" to “10" scale below, how distressing was the pain at the time you withdrew your hand?

0 ---------- 1 ---------- 2 ---------- 3 ---------- 4 ---------- 5 --------- 6 ---------- 7 --------- 8 ---------- 9 ---------- 10

Not distressing at all *Very severe distress*

Appendix 6

Échelle de douleur ischémique

Participant ID _____

Sur l'échelle de "0" à "10" ci-dessous, quelle était l'intensité de la douleur sensoriel au moment où vous avez retiré votre main?

0 ---------- 1 ---------- 2 ---------- 3 ---------- 4 ---------- 5 --------- 6 ---------- 7 --------- 8 ---------- 9 ---------- 10

Aucune douleur *Douleur la plus intense possible*

Sur l'échelle de "0" à "10" ci-dessous, à quel point la douleur vous a-t-elle incommodée au moment où vous avez retiré votre main (valeur affective de la douleur) ?

0 ---------- 1 ---------- 2 ---------- 3 ---------- 4 ---------- 5 --------- 6 ---------- 7 --------- 8 ---------- 9 ---------- 10

Aucunement incommodée *Sévèrement incommodée*

Appendix 7

BP and Hearth Rate Participant ID_____

Part 1. Basal. Measures of BP at 5 minutes interval. HR at the exact moment where BP measures are taken is also recorded.

	Blood pressure	**Hearth Rate**
Measure 1**		
Measure 2		
Measure 3#		

Part 2. Orthostatic Challenge. Measures of BP when laying down (i.e. at 2min, 4min). Participant stands up and more measures are taken after standing up (i.e. at 0min, 2min and 4min). HR at the exact moment where BP measures are taken is also recorded.

	BP	HR
Laying down (2min)**		
Laying down (4 min)		
Standing up (0 min)*		
Standing up (2 min)		
Standing up (4min)#		