OsteopathieSchule Deutschland

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# Which role has the autonomic nervous system in the generation and maintenance of Irritable Bowel Syndrome

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## I. Summary/Abstract


### Background

Irritable bowel syndrome (IBS) is a common disorder in today's society. Currently much research is being made in this area, but a major issue in the research is the complexity and variation of symptoms in different individuals which leads to researchresults that often differs between studies. Osteopaths claims to be able to, by treatment, influence the autonomic nervous system (ANS) and that is why this study is devoted to examine if there is a dysfunction of the ANS in IBS.

### Methods

PubMed database was searched with the keywords and Meshterms: Irritable bowel syndrome AND Autonomic nervous system. The articles used for this thesis were observational studies that were evaulated using the STROBE statement scale.

### Results

8 articles containing different methods to assess the ANS were selected for this thesis and they all showed that there are a dysfunction of the ANS, however which part of the ANS that were most affected differed between studies. 6 studys showed an increase of the activity in the SNS and one study showed an increase in the PSNS, the remaining study showed an alteration in the ANS activity without being able to define whether SNS or PSNS activity were higher.

### Conclusion

There is scientific support presented in these studies that show autonomic dysfunction in IBS-patients, but whether this is a cause or a consequence of the disease stands yet to be answered. Unclear is also which part of the ANS that is dominant, but most studies point to an increased sympathetic dominance. The reason of these divided researchresults is probably due to the fact that many different factors can affect IBS.



### Keywords

Irritable bowel syndrome, Autonomic nervous system, Osteopathy, Osteopathic medicine.

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## IV. List of abbreviations

ANS = Autonomic nervous system

CNS = Central nervous system

ENS = Enteric nervous system

FM = Fibromyalgia

GI-tract = Gastrointestinal tract

HC = Healthy controls

HPA = Hypothalamic Pituitary Axis

HR = Heart rate

HRV = Heart rate variability

IBS = Irritable bowel syndrome

MAP = Mean arterial pressure

PNS = Peripheral nervous system

PSNS = Parasympathetic nervous system

SNS = Sympathetic nervous system

# 1 Introduction

The irritable bowel syndrome (IBS) is classified as a functional disorder of motility in the small and large intestines and has been called the common cold of the stomach because of its high prevalence in the population. It is called a functional disorder because the abnormal muscle contractions of the intestines identified in people with IBS cannot be attributed to any identifiable abnormality of the bowel (Goodman *et* Snyder, 2000). Studies have shown that approximately between 10% and 20% of the general population is affected by this disorder, predominantly women. In the age interval between 20-50 years the prevalence is greatest. The prevalence is higher in unmarried compared to married individuals and also in unemployed compared to employed individuals (Andrews *et al,* 2005; Camilleri *et al*, 2002). IBS is not at all a life threatening condition, however, it can be very distressing for the patient and currently, the medical practitioners have no solution to the problem (Marcer *et* Parsons, 2006). Patients suffering from IBS often have non-gastrointestinal somatic symptoms and most experienced clinicians tends to use a holistic approach to diagnosis, observing features beyond the gut like previous history of medically unexplained symptoms, behavior, lethargy, headache, backproblems, dyspareunia and urinary symptoms (Whitehead *et al,* 2002). This knowledge is important for the doctor making the diagnosis since these features often is accompanied by IBS and the patient can avoid unnecessary examinations and referring to different specialties (Spiller, 2007). Emotional or psychologic responses to stress have a profound effect on brain chemistry, which in turn influences the enteric nervous system (Mayer, 1995). Although there is little evidence to support stress as cause, it is often implicated as an exacerbating factor (Sapolsky, 1998). Patients with IBS are known to have a higher incidence of mood disturbances, anxiety, depression, somatization disorders, and psychologic distress (Manabe *et al,* 2009).

IBS is a very complex syndrome and is believed to originate from a combination of dysmotility, visceral hypersensitivity, mucosal immune dysregulation, alterations of bacterial flora, and Central nervous system (CNS) - Enteric nervous system (ENS) dysregulation. The contribution of these factors may vary across different individuals or within the same individual over time (Drossman, 2006).

Defecatory disturbance in IBS can be diarrhea or constipation and in some case the two alternate over time. In pathophysiology research and clinical trials, a pain/discomfort frequency of at least 2 days a week during screening evaluation is recommended for subject eligibility (Drossman, 2006). There are no clear biological markers existing for IBS but visceral hypersensitivity is one of several supposed biomarkers, a considerable amount of IBS patients proves to have increased sensitivity to stretching force of the wall of the intestine in the recto-sigmoid area and this hypersensitivity seems to extend all the way up to the esophagus (Manabe *et al,* 2009; Wood, 2013). The pathophysiology of IBS is still clouded by many obscurities but it has been suggested that the autonomic nervous system (ANS), via neurological pathways of the ENS, is involved in the alteration of visceral sensitivity and that the CNS, via the same pathways, can influence secretory activity and motility of the gastrointestinal tract (GI-tract), to augment this suggestion subtle abnormalities in the ANS has also been found as an underlying factor in IBS patients (Manabe *et al,* 2009). Since osteopaths claims to be able to affect the autonomic nervous system with their treatment, this thesis will evaluate how important the autonomic component is in irritable bowel syndrome and this knowledge is valuable when it comes to osteopathic treatment of this type of gastrointestinal disorders. Depending on how much the autonomic nervous system is involved the osteopath can decide how much focus that is appropriate to put on treating areas related to, and affecting, the ANS in a treatment session.

# 2 Background

## 2.1 The IBS diagnosis

Most IBS patients have abdominal pain or discomfort intermittently, with flares lasting 2–4 days. Other symptoms include bloating, abnormal stool frequency, and abnormal defecation (Hahn *et al,* 1998). Patients can be subdivided according to stool consistency into: (1) IBS with constipation, in which patients have hard stools more than 25% of the time and loose stools less than 25% of the time; (2) IBS with diarrhoea, with loose stools more than 25% of the time and hard stools less than 25% of the time; and (3) IBS-mixed, with both hard and soft stools more than 25% of the time. Around a third of the patients have functional dyspepsia and many IBS patients also experiences their symptoms to get aggravated by meals. Patients can shift (about 33%) from one subtype to another over months or years and these are called alternators (Spiller, 2007). Henry D Janowitz, a U.S. gastroenterologist and a pioneer in establishing this field, who was president of the American Gastroenterological Association and played a major role in founding the Crohn's and Colitis Foundation of America, lists in his book the symptoms of IBS, based on his years of clinical experience as: a) abdominal pain relieved by having a bowel movement; b) looser and more frequent bowel movements associated with the abdominal pain; c) bloated and distended abdomen or a feeling that the abdomen is swollen; d) a sensation that the bowel is not completely emptied after a movement. He also states that the predominant symptoms of IBS are abnormal defecation and abdominal pain and that these symptoms might get worse if the patient is subdued to emotional or physical stress (Janowitz, 1989).

The diagnosis IBS were traditionally based on the absence of any other abdominal pathology but as a development of this the Manning criteria were created:

Manning criteria for irritable bowel syndrome:

- Pain relieved by defecation
- More frequent stools at the onset of pain
- Looser stools at the onset of pain
- Visible abdominal distension
- Passage of mucus

- Sensation of incomplete evacuation (Camilleri *et al*, 2002)

As further development of the Manning criteria different versions of the Rome criteria were created. Today there are three versions of Rome criteria: Rome I, Rome II and Rome III. Rome IV criteria is expected to be released in 2016.

Rome III criteria for irritable bowel syndrome:

Recurrent abdominal pain or discomfort* at least 3 days/month in the last 3 months associated with *two or more* of the following:

1. Relieved with defecation; and/or

2. Onset associated with a change in frequency of stool; and/or

3. Onset associated with a change in form (appearance) of stool

Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

* “Discomfort” means an uncomfortable sensation not described as pain.

The Rome criteria were created to facilitate for the clinician to make a diagnosis of irritable bowel syndrome without having to put the patient through invasive diagnostic procedures and expensive, time-consuming examinations. When the so called ”red flags” (nocturnal symptoms, rectal bleeding, abdominal abnormalities on physical examination, fever, anemia, weight loss, family history of colon cancer) are ruled out, the specificity of diagnosing with these criteria are high, even as high as 98% according to studies (Vanner *et al*, 1999).

### 2.2 The basic organisation of the nervous system

Understanding neurology is fundamental for understanding the pathophysiology of IBS hence a brief description of the nervous system follows.

The function of the nervous system is to control and regulate many body activities both locally and globally in the body. It acts rapidly and enables the body to react to constantly ongoing changes of its internal and external environments (Marcer *et*

Parsons, 2006).

The nervous system is separated into two structural divisions:

- Central nervous system: brain and spinal cord
- Peripheral nervous system (PNS): somatic, autonomic, and enteric nerves in the periphery

Functionally the nervous system is divided in the autonomic, somatic and enteric nervous system. The interaction between these different functional parts of the nervous system is mainly what osteopaths effects when treating patients (Marcer *et* Parsons, 2006). The PNS is constructed of nerve cells which are afferent (sensory) and sends information to the CNS via the dorsal horn of the spinal cord, or efferent (motor) which sends impulses from the CNS or ganglia (collections of neurons outside the CNS) to target (effector) cells; somatic efferent axons (nerve cells) target skeletal muscle and visceral efferent axons target smooth muscle, cardiac muscle, and glands. These impulses exits the spinal cord via the ventral horn and through a spinal nerve (Netter *et al,* 2010). From the spinal cord exits 31 pair of spinal nerves and from the brain and brainstem exits 12 cranial nerves, when the nerve impulse enter these it has left the CNS and is located in the PNS. The cranial nerves have some unique functions and can be both somatic and visceral (Netter *et al,* 2010).

The somatic nervous system consists of sensory and motor fibers to skin, skeletal muscles and joints. The ANS has components in both the CNS and the PNS, the major autonomic components of the CNS includes the Limbic forebrain, Hypothalamus, several brainstem nuclei and the intermediolateral cell column of the spinal cord (Chila *et al,* 2011). The autonomic components of the PNS include numerous ganglia (collections of neuron cell bodies located outside of the CNS) and a network of fibers distributed to all tissues of the body with the exception of the hyaline cartilages, the centers of the intervertebral disks, and the parenchymal tissues of the CNS (Chila *et al,* 2011). ANS is divided into a sympathetic branch (sympathetic nervous system, SNS) and a parasympathetic branch (parasympathetic nervous system, PSNS) and these two branches consists of sensory and motor fibers to all smooth muscle (including viscera and vasculature), cardiac muscle (heart) and glands (Netter *et al,* 2010). ANS is a two-neuron system with a pre-

ganglionic neuron in the CNS that sends its axon into a peripheral nerve to synapse (connect) on a postganglionic neuron in a peripheral autonomic ganglion. This two-neuron system does not exist in the somatic nervous system where there is only one neuron that stretches all the way from the spinal cord to the effectorcell (skin, skeletal muscle or joint). The postganglionic neuron then sends its axon to the target (smooth muscle, cardiac muscle, and glands). The ANS is a visceral system, since many of the body's organs are composed of smooth muscle walls or contain secretory glandular tissue (Chila *et al,* 2011).

The SNS has two major components: vascular and visceral. The innervation of fascia, smooth muscle of vasculature and hair follicles plus secretory sweat glands in the skin is made by the vascular component and the nerve impulses is sent via the spinal nerves. The visceral component innervates smooth muscle of the gut, cardiac muscle, nodal tissue and glandular organs of the thoracic, abdominal, pelvic and perineal viscera (Chila *et al,* 2011). In the SNS preganglionic neurons only exists in the T1-L2 spinal cord level hence the sympathetic nervous system is also known as the thoracolumbar outflow (Marcer *et* Parsons, 2006). The preganglionic axon leaves the spinal cord via a ventral root, and then enter a spinal nerve and continues via a white ramus communicans to enter the sympathetic chain. The sympathetic chain, which also can be called the sympathetic trunk, is a bilateral chain of ganglia just lateral to the vertebral bodies that runs from the base of the skull to the coccyx, the location of these ganglias near the vertebras has given them the name of the paravertebral ganglias (Chila *et al,* 2011). When the preganglionic axon has entered the sympathetic chain it can behave differently and has four options: They may synapse at that level with a postganglionic fibre that will then pass on to its target viscus. They may pass through the ganglion without synapsing and pass to a sympathetic ganglion closer to their target viscus where they will synapse with a postganglionic fibre. They may ascend or descend within the sympathetic chain and synapse at a level different to their exit level. They may ascend or descend within the sympathetic chain without synapsing and then exit to pass to a sympathetic ganglion closer to their target viscus where they will synapse (Netter *et al,* 2010). It is by ascending or descending in the sympathetic chain that the preganglionic fibers can reach areas of the spine that anatomically lies above and below T1 and L2 levels, meaning the cervical, lower lumbar and

sacral regions. When the axon leaves the sympathetic chain it can either go back to a spinal nerve or go via a splanchnic (visceral) nerve to reach its final destination (Marcer *et* Parsons, 2006). Axons of preganglionic fibres that goes straight through the sympathetic chain into the body and creates ganglia, the para aortic ganglia, the coeliac, mesenteric and hypogastric ganglias are the biggest ones and together they are called the prevertebral ganglias (Marcer *et* Parsons, 2006).

The parasympathetic nervous system is also a two-neuron system with its preganglionic neuron in the CNS and postganglionic neuron in a peripheral ganglion, the preganglionic axons are to be found in cranial nerves 3,7,9 and 10 and in the sacral spinal cord at the level of S2-S4 hence the neurons lies in the cranial nuclei associated with the mentioned cranial nerves and in the lateral gray matter of the spinal cord at levels S2-S4 (Netter *et al,* 2010). Because of the cranial and sacral location of the outflow of the preganglionic neurons in the PSNS it is also called the craniosacral outflow (Marcer *et* Parsons, 2006). A difference compared to the SNS is that the PSNS only innervates visceral organs and blood vessels in the head, neck, thorax, abdomen and pelvis hence PSNS does not innervate the peripheral vasculature of the extremities and trunk (Chila *et al,* 2011). Preganglionic parasympathetic axons (with exception of cranial nerve no.10 - the vagusnerve) may either pass to a peripheral ganglion in the head (ciliary, pterygopalatine, submandibular, and otic ganglia) and synapse to a postganglionic neuron which in turn innervates smooth muscle and glands of the head, or the axons exit the sacral spinal cord via a ventral root and enter the pelvic splanchnic nerves to synapse on postganglionic neurons in terminal ganglia located in or near the viscera to be innervated and afterwards pass to its effector cell (Netter *et al,* 2010). The vagus nerve is different compared to the other parasympathetic cranial nerves, its preganglionic fibers innervates ganglia in the wall of the organs of the cervical, thoracic, and superior portions of the GI-tract approximately down to the splenic flexure of the colon and from these ganglia postganglionic fibers innervates the smooth muscle layers and glands of the organ (Chila *et al,* 2011). The vagal preganglionic axons takes its course via the celiac ganglia and the superior mesenteric ganglia to reach its terminal organ and the pelvic splanchnics route goes through the inferior hypogastric plexus (pelvic plexus), which is located in the endopelvic fascia. Through this plexus, the preganglionic axons can reach the visce-

ral organs of the pelvic basin such as the urinary bladder, the internal reproductive organs, and the rectum whereas the inferior mesenteric plexus is passed to reach the descending and sigmoid colon (Netter *et al*, 2010).

Broadly, the function of the ANS is that the SNS prepares the body systems for action which includes sending more blood to the skeletal muscles whereas the PSNS has a more calming role where the body prioritizes digestion etc. (Marcer *et* Parsons, 2006).

The enteric nervous system is originally considered as a part of the autonomic nervous system but nowadays it is usually said that to be plexuses and ganglia of the gastrointestinal tract that regulate bowel secretion, absorption, and motility; linked to the autonomic nervous system for optimal regulation (Netter *et al*, 2010). It consists of the Auerbach´s (also called myenteric plexus) and Meissner´s (also known as submucosal plexus) plexuses found throughout the wall of the GI-tract. It affects motility by controlling the secretion of glands in the GI-tract which in turn cause digestion and mucous production. The ENS allows the GI-tract to function independently of the rest of the nervous system, however, it may be greatly influenced by the autonomic nervous system (Marcer *et* Parsons, 2006). If the sympathetic activity increases, which it does when the patient is exposed to stress, this lowers or shuts down the activity of the enteric nervous. The opposite happens in rest, when the parasympathetic activity increases (Kuchera *et* Kuchera, 1994). Optimal GI functioning requires coordinated interactions of the ANS, the enteric nervous system, and the endocrine (hormonal) system (Marcer *et* Parsons, 2006).

### 2.3 Osteopathic considerations of the nervous system

ANS is primarily involved with the day-to-day automatic functions of the visceral processes of the body and is ultimately controlled by the brain and brainstem structures. At segmental level in the spinal column nerve cells called interneurons exists, they connect nerve cells to each other and has the ability to transmit afferent nerve impulses directly to an efferent nerve cell without the impulse necessarily having to go via ascending nerve pathways in the spinal cord to the brain hence making the individual aware of it, there also are examples when the afferent fiber connects to the efferent without an interneuron between as well. The same

goes for the somatic nervous system and this is called a reflex arc, it enables automatic responses to a stimulus from either muscles, skin or connective tissue, in the somatic nervous system, or from viscera in the ANS (Chila *et al,* 2011). When both the sensory receptor and the motor effector are located in the somatic system, which is the same as the musculoskeletal system, the reflex is in osteopathic terms called a somaticosomatic reflex and when they are located in the visceral system the reflex is called a viscerovisceral reflex meaning for example that the presence of food in the stomach makes local receptors in the organ start sending impulses to the related segment of the spinal cord via afferent axons of the reflex arc, which in turn will cause the effector glands to increase secretion. Viscerovisceral reflexes are mediated via the ANS and somaticosomatic reflexes are mediated via the somatic nervous system (Marcer *et al,* 2006).

Viscerosomatic reflexes

For the osteopathic practitioner concerning palpatory diagnosis and treatment, knowing the ANS anatomy is of high importance due to the assumption that an increase of afferent input from somatic structures (because of pathology or dysfunction) can be expected to have an effect on visceral organs and vice versa because of what is called somatovisceral and viscerosomatic reflexes, this may in turn create tissue changes and dysfunction in neurologically related areas, for example a viscerosomatic dysfunction may create changes in paraspinal soft tissue segmentally related with sympathetic innervation to the dysfunctional organ (Chila *et al,* 2011). Osteopaths have known and used these reflexes in osteopathic treatment, in the belief that osteopathic manipulative techniques create a disruption of the viscerosomatic reflex arc and thereby enables for improvement of the underlying visceral dysfunction or disease, for many years but there are a lack of scientific studies supporting this theory. Licciardone *et al* tried to prove the relation between osteopathic palpatory findings associated with a particular chronic disease which in this case were type 2 diabetes mellitus. The results were that a potential explanation for a consistent finding of tissue changes at T11-L2 level on the right side in the diabetes group might involve viscerosomatic reflex arc but might just as well be a false association depending on other visceral dysfunctions or simply just a chance observation, so larger prospective studies were suggested

(Licciardone *et al,* 2007).

### 2.4 Pathophysiology of IBS

The pathophysiology of IBS is still very much unclear and there is a lack of biological markers for the condition but studies have at least found some attributes to be more consistently appearing in IBS patients (Manabe *et al,* 2009). Most likely the pathophysiology involves both central and peripheral mechanisms. Central mechanisms include anxiety, depression and somatisation while peripheral dysfunction is characterized by changes in gut motility and secretion as well as visceral hypersensitivity (Barbara *et al,* 2011). A disruption of the so called brain-gut axis, which means a way of communication between sensory neurons in the GI-tract and motor response generated in the central nervous system, that provokes changes in digestive motility and secretion, causes visceral hypersensitivity and leads to cellular and molecular abnormalities in the enteroendocrine and immune systems has been suggested. In addition, genetic factors, infections and alterations of the intestinal microbiota, inflammation and food intolerance and/or hypersensitivity could play a role by altering the integrity of the intestinal barrier and increasing intestinal permeability (Spiller, 2007).

Alterations of intestinal motility

Studies examining the upper GI-tract (esophagus and stomach) has found that there is some relation between altered motility (movement of the intestines created by contraction of smooth muscles) and IBS but it seems more likely that altered motility of the upper GI-tract has a stronger relation to the presence of symptoms of upper GI-disorders like hiatus hernia, esophagitis, gastritis and reflux (Posserud *et al,* 2006). There are evidence for disturbed motility of the small intestines of IBS patients as a group but it has not been possible to find a uniform pattern of motility within this group or a consequent correlation between patient symptoms and alterations of motility. It is not clear wether the motility disturbances exists due to factors related to CNS or ENS but there are evidence indicating that both of them are involved (Kellow *et al,* 1992; Posserud *et al,* 2006). Concerning the colon there are similarities with the small intestines regarding alterations of motility, no uniform motility pattern has been found but evidence shows that there are alterations of

motility compared to healthy controls. It seems that exaggerated colonic response to stimuli, like food and perhaps also stress and emotions, which together with visceral hypersensitivity can be devastating for the patient, may anticipate the symptomatic picture of the patient. Alterations in gastrointestinal reflex activity among IBS patients appears to be generally accepted but more studies is required in this area as well (Posserud *et al,* 2006).

Visceral hypersensitivity

It is well recognized that visceral hypersensitivity can occur due to (1) sensitization of primary sensory afferents (nerve cells) innervating the viscera, (2) hyperexcitability of spinal ascending neurons (central sensitization) receiving synaptic input from the viscera, and (3) dysregulation of descending neural pathways that modulate spinal nociceptive (pain) transmission. (Sengupta, 2009). Lowered perception thresholds for balloon distension in IBS patients have been demonstrated in the rectum and colon, as well as in the esophagus, stomach and the small intestine. These findings support a generalized enhancement of gastrointestinal sensitivity in IBS patients. It is unclear whether IBS patients have a general hypersensitivity since divergent results exist regarding somatic sensitivity (Posserud *et al,* 2006).

Dysfunctional gas transit

Many IBS patients complains over bloating and experiences that they have too much gas in their abdomen which in turn causes abdominal pain and this has been proposed to be secondary to disordered intestinal motility in combination with visceral hypersensitivity (Posserud *et al,* 2006). A large proportion of patients with IBS have been shown to have impaired transit and tolerance of intestinal externally induced gas which reproduced their symptoms. This dysfunctional gas transit may represent a possible mechanism of IBS symptoms, specifically pain and bloating (Serra *et al,* 2006). Of great interest, especially for the osteopath who's treatment is aiming to improve posture, it has been proven that physical activity and body posture can improve abdominal gas transit (Dainese *et al,* 2004; Dainese *et al,* 2003). Later studies have shown that in patients reporting bloating, the small bowel is the gut region most responsible for ineffective gas propulsion (Salvioli *et*

*al,* 2005). However, the proximal region of colon is important as well regarding areas responsible for bloating (Hernando-Harder *et al,* 2010).

To sum up, IBS patients does not seem to produce more gas than a healthy person but can still have gas related symptoms because of dysfunction in the transit of gas combined with visceral hypersensitivity (Posserud *et al,* 2006).

### Affected gastrointestinal secretion

Gastrointestinal secretion is difficult to measure in studies hence there are not many clinical trails performed in the area but there are some that indicates that abnormal gut water secretion. The densities of some peptides (biological molecules) mediating gut motility, secretion and sensation, *e.g.*, serotonin, peptide YY, pancreatic polypeptide, enteroglucagon, somatostatin, *etc*. were reduced in the colon of IBS patients and it seems like abnormal gut water secretion is one of many possible contributing factors in the development of IBS (El-Sahly *et al,* 2012). There are also some evidences supporting altered secretion in the small intestine of IBS patients (Posserud *et al,* 2006).

### Gastroenteritis

A prior history of bacterial or viral gastroenteritis may play an important role as a trigger in the development of IBS (Konturek *et al,* 2011). A review of postinfectious irritable bowel syndrome made by Halvorson *et al* came to the conclusion that there is a sevenfold increase in the risk of developing functional bowel disorders, like IBS, following gastrointestinal infection (Halvorson *et al,* 2006). There are studies presenting an abnormal number of bacteria in the small intestine in IBS patients and this results in small intestinal bacterial overgrowth which in turn can be caused by abnormal small intestinal motor function, if this is a cause of IBS or not is not known but it is very possible it can lead to an infection which, as stated earlier, increases the risk of developing IBS (Posserud *et al,* 2006).

Brain-gut axis

The brain-gut axis is explained in simple terms as bidirectional pathways linking emotional and cognitive centers in the brain with visceral afferent sensation and intestinal function, this bidirectional system includes hypothalamic- pituitary- adrenal (HPA) axis with important effects on GI motility, sensation and immune function, and also the communication between CNS and the gut via the ANS (sympathetic and parasympathetic pathways) by modulation of the ENS (Spiller, 2007). Comparing IBS patients and healthy controls has shown differences in activation of pain processing areas in the brain (anterior cingulate cortex, thalamus, insula and prefrontal cortex) between the two groups (Hobson *et* Aziz*,* 2004). There are studies showing alterations in different areas of the brain-gut axis in IBS patients but the results are inconclusive (Posserud *et al,* 2006) Osteopathy is a manual therapy which places emphasis on normal mobility of tissues. It respects the interrelationship of mind and body and recognizes that the human body functions as a dynamic unit. This fits perfectly with the concept of the the brain-gut axis. It seems likely that the different osteopathic treatment modalities are able to intervene at different levels of this brain-gut axis (Hundscheid *et al,* 2007). This study will further focus on the ANS as a part of the brain-gut axis and try to evaluate how important this part is in the pathophysiology of IBS.

## 2.5 Different methods of treatment of IBS

Important factors regarding IBS patients is to offer an explanation of their condition, reassurance and lifestyle advice is important as well, more than 50% of patients visiting the doctor at the first consultation believes they have serious disease and to reassure them that this is not the case is the first and very important step in the treatment (Spiller, 2007). Most patients have tried, on their own before seeing the doctor, different modifications of their diet, in many cases unsuccessfully. One study came to the conclusion that almost half of the patients participating had symptom improvement from a strict diet for three weeks but it is unclear how much of this that was placebo, dairy products and wheat were the products that the greatest part of the participants responded negatively to (Nanda *et al,* 1989). Psychological treatment might help those patients believing that stress is an im-

portant factor, but studies performed could not prove much change in bowel symptoms (Spiller, 2007). Hypnotherapy has been proven to have short-term effect in significantly alleviate overall gastrointestinal symptoms in IBS patients. More studies is needed to evaluate the long-term effect of hypnotherapy (Lee *et al,* 2014). Some IBS patients turns to homeopathy for help but there are few studies performed and those existing mostly lacks important information of data, high or unknown risk of bias, short-term follow-up (Peckham *et al,* 2014). Acupuncture may be the choice of therapy for others but sham-controlled RCTs have not been able to find any benefits of acupuncture relative to a credible sham acupuncture control for IBS symptom severity or IBS-related quality of life (Manheimer *et al,* 2013). Many patients prefer drug therapy which is what most doctors recommends and the only help the public medical care can provide, besides lifestyle advice, but in most RCTs evaluating this therapy the true effect of drug therapy is smaller than the placebo effect and the need for more effective remedies for IBS is substantial, however antispasmodics might relieve abdominal pain, Serotonin type 3 antagonists may improve diarrhoea or constipation and pain, tricyclic antidepressants possibly improves pain especially in diarrhoea-predominant patients (Spiller, 2007). Currently there are more agents than ever before available for gastroenterology practitioners to treat symptoms related to IBS but, despite progress in the understanding of IBS pathophysiology, there still does not exist any targeted treatment (Wall *et al,* 2014).

### 2.6 Osteopathic considerations in IBS

Kuchera states that osteopaths have been using viscerosomatic reflexes to aid them in their diagnosis of different visceral diseases and dysfunctions for over 100 years (Kuchera *et* Kuchera, 1994). Osteopaths consider themselves to be able to, by treatment, affect the autonomic and enteric nervous system in the patient. To be able to do this, the osteopath consider some areas of the spine, where nerves from the sympathetic nervous system has its outflow to the intestines, to be very important. These levels of the spine is generally from thoracic vertebra number 7 to lumbar vertebra number 2 (Netter *et al*, 2010). Conversely, the parasympathetic outflow via the vagus nerve and the pelvic splanchnic nerves will be important, this includes the suboccipital area, the carotid sheath and mediastinum for the vagus

nerve and the level of sacral vertebra number 2-4 plus the sacroiliac joints for the pelvic splanchnic nerves (Marcer *et* Parsons, 2006). Other important areas in osteopathic treatment of IBS, by affecting the autonomic nervous system, is the autonomic plexuses, namely the celiac plexus, superior and inferior mesenteric plexuses and the superior and inferior hypogastric plexuses, primarily because of their role in influencing the enteric nervous system (Kuchera *et* Kuchera, 1994). One of the main principles in osteopathy is the interrelationship of structure and function and the osteopathic treatment and diagnosis relies on manual contact with the patient, treatment consists of gentle stretching, mobilizing and manipulation of body tissues (musculoskeletal and visceral) with the aim to restore physiological motion hence blood and lymph flow and in turn tissue health (Hundscheid *et al,* 2007). Osteopathy is a holistic approach and focuses on the whole person instead of just the symptoms which means that the treatment will be individualized for each patient, regarding IBS an important part of the treatment will to make sure that the abdominal organs have satisfying mobility in relation to surrounding structures and peritoneal suspension mechanisms and attachments (Hundscheid *et al,* 2007). Dysfunction in the connections between the brain and the gut which broadly is composed of the ANS and ENS seems to be involved in IBS and this makes osteopathic treatment to an interesting choice of therapy, Hundscheid *et al* conducted a randomized clinical trial in 2007 comparing standard care and osteopathic treatment of IBS patients and the results were very uplifting for the patients in the IBS group, 68% in the osteopathic group experienced definite overall improvement in symptoms and 27% showed slight improvement compared to 18% definite and 27% slight improvement in the standard care group (Hundscheid *et al,* 2007). It should be in the interest of osteopathy to clarify the role of the ANS in IBS since this is an important part of the osteopathic treatment regarding the brain-gut axis and to examine this role is the aim of this study.

# 3 Question

Is there evidence for a dysfunction of the autonomic nervous system in patients with irritable bowel syndrome compared to healthy controls?

# 4 Methodology

## 4.1 Type of study

The thesis is a systematic literature overview and scientific articles have been analysed according to the STROBE Statement which is a checklist of 22 items that should be included in reports of case-control studies such as important information in the introduction, clarity of aim and objectives, detailed information about participants and how the data was measured and handled in the statistical analysis and efforts to address potential bias etc. See appendix 9.1 (Vandenbroucke *et al*, 2007).

## 4.2 Articles

### 4.2.1 Inclusion and exclusion criteria

**Inclusion criteria**: Observational studies published in well known scientific peer reviewed journals which examines the relationship between irritable bowel syndrome and the autonomic nervous system will be qualified to be analysed. The IBS-patients in the articles must be diagnosed by ROME or Manning criteria. The articles must be written in english or swedish.

**Exclusion criteria**: Studies that focuses on issues like relationship between irritable bowel syndrome and for example migraine will be excluded as well as studies that involves animals. Studies with treatmentintervention of medications or complementary medicin like for example osteopathy, homeopathy or acupuncture were excluded. Articles focusing on the relationship between IBS and anorexia or depression were also excluded. Studies more than 20 years old were considered to old to be analysed.

### 4.2.2 Literature search

Relevant studys were identified by performing a literature search of PubMed in may 2014 with the Mesh and boolean terms: Irritable bowel syndrome AND Autonomic nervous system NOT animals NOT migraine. This resulted in 66 hits and 4 of these articles qualified to be used in this study, 4 other articles used in this study were found in the referenses of theese articles. The Cochrane Library was also

searched with the same keywords but no new articles of interest were found there. Mesh terms Irritable bowel syndrome AND heart rate were also used searching Pubmed and Cochrane Library since heart rate variabilty is commonly used to measure autonomic activity but no new articles were found during this search either, only 2 of the articles found during the first search. Google scholar was also searched with the same keywords and boolean terms but no new articles that met the inclusioncriteria of this study were found. The filter humans was used in all searches on Pubmed.

### 4.2.3 Table 1. Searchresults

| Searchwords | Pubmed | Cochrane Library | Articles used |
|---|---|---|---|
| Irritable bowel syndrome AND autonomic nervous system NOT animals NOT migraine | 66 | 8 | 4 |
| Irritable bowel syndrome AND heart rate | 30 | 3 | 2 |

## 4.3 Timetable

**April 2014:** Brief search of articles related to the question of the thesis

**May/June:** Searching and reading of relevant articles

**July/August:** Writing of background

**August/September:** Analysing of articles and writing of results part

**September/October:** Writing of discussion part

**October:** Creating of poster

# 5 Results

Table 2 is a summary of the 8 articles that were used in this study. It also shows the result of the study regarding the ANS, meaning that ↑ SNS is an increase of the activity in the sympathetic nervous system and ↓ SNS is a decreased activity. Same applies for the PSNS.

**Table 2**

| Study & Year | Journal | Number of participants with IBS | ANS attribute | STROBE statements not fulfilled |
|---|---|---|---|---|
| 1.Mazur *et al* 2012 | Medical science monitor | 30 | ↑ SNS Disturbed PSNS activity | 1a, 5, 9, 10, 12c,13b, 14a,b, 19, 22 |
| 2.Chalay *et al* 2012 | Clinical journal of pain | 13 | Mild ↑ SNS | 1a, 5, 10, 12c,e, 13a,b, 14a, 22 |
| 3.Burr *et al* 2000 | Biological research for nursing | 106 | ↑ SNS ↓PSNS | 1a, 10, 22 |
| 4. Tousignant Laflamme *et al* 2006 | Journal of clinical gastroenterology | 14 | ↑PSNS ↓SNS | 1a, 10, 12c, 13a,b,14b |
| 5. Hattori *et al* 2010 | Neurogastroenterology and motility | 12 | Altered ANS responses | 1a, 12c, 13a,b, 14b |

| Study & Year | Journal | Number of participants with IBS | ANS attri-bute | STROBE statements not fulfilled |
|---|---|---|---|---|
| 6. Gupta *et al* 2002 | Digestive Diseases and Sciences | 20 | ↑ SNS<br>↓PSNS | 1a, 5, 10, 12c, 13a,b, 14a,b, 19, 22 |
| 7. Heitkem-per *et al* 1998 | Digestive Diseases and Sciences | 25 | ↑ SNS<br>↓ PSNS | 1a, 13b, 14b, 22 |
| 8. Tillisch *et al* 2005 | Gut | 46 | ↑ SNS<br>↓ PSNS | 1a, 5, 9 10, 14, 19 |

**1. Autonomic nervous system activity in constipation- predominant irritable bowel syndrome patients (2012)**

**Authors:** Marcel Mazur, Agata Furgała, Konrad Jabłoński, Tomasz Mach, Piotr Thor

**Aim:** The aim of this study was to evaluate changes in ANS activity and its correlation with gastric myo- electric activity in constipation-predominant IBS patients.

**Methods:** Resting and functional autonomic nervous system tests and percutaneous electrogastrography were performed to measure heart rate variability (HRV), the tilt test, the hand grip test and the valsalva manouvre on 30 patients with a diagnosis of constipation- predominant IBS and 30 healthy volunteers. Fasting plasma hormone levels were also measured in both groups (adrenalin, noradrenalin, insulin, ghrelin and cholecystokinin).

**Results:** Increased sympathetic activation with disturbed parasympathetic function was demonstrated. Substantially higher concentration of plasma catecholamines in IBS-patients confirms sympathetic overbalance. Abnormal hormonal levels found in IBS- patients may influence intestinal motility and disturb the brain-gut axis. Gastric myoeletrical activity disturbances may result from lack of sympatho-parasympathetic equilibrium. Resting HRV parameters were lower in IBS patients in comparison with the control group. Analyses of ANS activity indices revealed abnormal value of 30/15 ratio in the patient group ($p<0.05$) indicating parasympathetic dysfunction.

**Conclusion:** Central sympathetic influence within the brain-gut axis is most probably responsible for myoelectrical activity disturbances in irritable bowel syndrome patients (Mazur *et al,* 2012).

STROBE statements failed to be achieved: 1a, 5, 9, 10, 12c, 13b, 14ab, 19, 22 (Vandenbroucke *et al*, 2007).

## 2. Comparing Pain Modulation and Autonomic Responses in Fibromyalgia and Irritable Bowel Syndrome Patients (2012)

**Authors:** Philippe Chalaye, Philippe Goffaux, Patricia Bourgaul, Sylvie Lafrenaye, Ghislain Devroede, Alain Watier, Serge Marchand

**Aim:** To compare descending pain inhibition, pain sensitivity, and ANS reactivity to pain in fibromyalgia (FM), IBS, and healthy controls.

**Methods:** Female patients with FM (n=10), IBS (n=13), and HCs (n = 10) were exposed to multiple cold water (12°C) immersions of one arm to study pain sensitivity and descending pain inhibition. The arm was divided into 4 segments: (1) fingers (second phalanges); (2) wrist; (3) elbow; and (4) shoulder. Each segment was immersed for a period of 2 minutes and was followed by a 5 minutes resting period. Electrocardiograms (ECG) were recorded and analyzed only during the finger immersion period. HRV was also assessed during immersions.

**Results:** Heart rate variability analyses confirmed that, in response to mild levels of pain, patients with FM showed greater sympathetic activity whereas HCs showed greater parasympathetic activity. Patients with IBS showed intermediate ANS responses. Pain intensity scores were highest in FM, intermediate in IBS, and smallest in HCs. In contrast, pain inhibition was absent in FM, intermediate in IBS, and strongest in HCs. Importantly, controlling for differences in pain inhibition abolished group differences in pain sensitivity.

**Conclusion:** Compared to HCs both IBS and FM had increased somatic pain sensitivity and this despite the fact that the testing was performed on the upper-body dermatomes which are not related to gastrointestinal dermatomes. IBS responded to the cold pressor test with less sympathetic activity than patients with FM and less parasympathetic activity than HCs. This intermediate autonomic response parallels the modest amount of hyperalgesia and pain inhibition observed among patients with IBS, and again argues that processing changes are less pronounced among patients with IBS than FM (Chalaye *et al,* 2012).

STROBE statements failed to be achieved: 1a, 5, 10, 12c,e, 13a,b, 14a, 22 (Vandenbroucke *et al*, 2007).

**3. Comparison of Autonomic Nervous System Indices Based on Abdominal Pain Reports in Women with Irritable Bowel Syndrome (2000)**

**Authors:** Robert L. Burr, Margaret Heitkemper, Monica Jarrett, Kevin C. Cain

**Aim:** Determine whether self-reported abdominal pain intensity and the presence of postprandial pain are related to HRV measures of systemic autonomic activity.

**Methods:** 106 IBS-patients (women) and 41 controls (women) completed bowel symptom and psychological distress questionnaires and wore 24-h Holter electrocardiogram moni- tors to estimate global heart rate variability measures of parasympathetic activity and sympathetic nervous system/parasympathetic nervous system balance.

**Results:** About one-third of the IBS sample reported severe or very severe abdominal pain (n = 34/106), and about one-half of the IBS sample reported postprandial pain (n = 52/106). Even after statistically controlling for age, body mass index, and psychological distress, vagal heart rate variability measures were markedly lower in women reporting high pain ($P < 0.01$) and markedly higher in women reporting postprandial pain ($P < 0.02$).

**Conclusion:** The vagal component (PSNS activity) of heart rate variability appears to be reduced in women with severe abdominal pain, especially in those whose pain is not postprandial (Burr *et al,* 2000).

STROBE statements failed to be achieved: 1a, 10, 22 (Vandenbroucke *et al*, 2007).

**4. Different Autonomic Responses to Experimental Pain in IBS Patients and Healthy Controls (2006)**

**Authors:** Yannick Tousignant-Laflamme, Philippe Goffaux, Patricia Bourgault, Serge Marchand

**Aim:** The main goal of this study was to examine and describe autonomic reactivity to a painful somatic stimulus using various indicators of ANS activity in IBS patients compared with HCs.

**Methods:** 27 women, 14 IBS, and 13 healthy controls (HCs), were exposed to a cold water (7°C) immersion test of the forefoot for 2 minutes. Pain perception, galvanic skin responses (GSR) which measures fluctuations in skin conductance evaluating peripheral sympathetic response as a function of sweat gland activity, and heart rate (HR) were monitored during and after the immersion. Subjects rated their perceived pain every 15 seconds for the 2-minute immersion. Ratings of pain intensity and unpleasantness were obtained using a separate visual analog scale with numeric and verbal descriptors ranging from 0 to 100. The foot were used because of shared somato-visceral convergens on spinal level with the viscerotome of colon.

**Results:** The peak rise in heart rate (HR) was significantly higher ($P<0.02$) for HCs during immersion (22%) than it was for IBS-patients (8%). HRV analysis showed opposite autonomic cardiac reactivity to pain in HCs and IBS-patients, IBS had increased parasympathetic/decreased sympathetic reactivity.

**Conclusion:** The results of the painperceptiontesting showed normal somatic sensitivity in IBS-patients meaning no hypersensitivity but changes in HR, HRV and GSR-reactivity demonstrated increased parasympathetic and decreased sympathetic activity which means that IBS patients have different cardiac and autonomic responses to a nociceptive somatic stimulus but normal sensitivity (Tousignant-Laflamme *et al,* 2006).

STROBE statements failed to be achieved: 1a, 10, 12e, 14a, 22 (Vandenbroucke *et al*, 2007).

**5. Differential responding of autonomic function to histamine H1 antagonism in irritable bowel syndrome (2010)**

**Authors:** T. Hattori, S. Watanabe, M. Kano, M. Kanazawa, S. Fukudo

**Aim:** Investigate the pathophysiology of IBS by examining the role of neuronal histamine in the ANS of controls and IBS subjects. Two additional hypotheses were also tested: (1) visceral stimulation differentiates ANS function between IBS subjects and controls; and (2) hypnotic suggestion modulates autonomic responses to visceral stimulation.

**Methods:** 12 IBS-patients and 12 controls, all males, were administered either 100 ug/kg chlorphenamine or saline on two different days, blinded of which substance they were exposed to during each visit. Chlorphenamine was administered to try to attenuate the effect of histamine which has two (peripheral and central) cardiovascular control actions. The peripheral action reduces vascular resistance and MAP while the central action induces a pressor effect which elevates MAP and HR. The rectum was stimulated with electrical currents of 0 mA (sham) or 30 mA. Autonomic nervous system function was measured using mean arterial pressure (MAP), HRV and plasma catecholamines and histamine. In the hypnotic induction indirect suggestions for the modulation of pain (increase: hyperalgesic; decrease: analgesic) were used by giving suggestiones consisting of words to distract from the rectal stimulation and decrease abdominal pain. The neutral suggestion consisted of the same syllables as hyperalgesic or analgesic suggestions, but with meaningless words. Subjective perceived stress during the examination was evaluated on an ordinate scale.

**Results:** The MAP significantly increased after chlorphenamine administration in IBS subjects, but not in controls. Heart rate revealed a significant drug effect ($P < 0.001$), which decreased after chlorphenamine administration in controls, but not in IBS subjects. Perceived stress significantly increased by rectal stimulation ($P < 0.001$) in both groups and a significant stimulus and IBS interaction ($P < 0.05$) was revealed, indicating greater reduction in IBS subjects by chlorphenamine.

**Conclusion:** Sympathetic vasomotor tone in IBS subjects differentially responded on administration of a histamine H1 antagonist to that of controls. It is most likely that chlorphenamine affects HR and HF by inhibiting the central action of histamine. These findings suggest an increased histaminergic activity in IBS subjects. Neither of the two additional hypothesises were proven in this study (Hattori *et al*, 2010).

STROBE statements failed to be achieved: 1a, 12c, 13a,b, 14b (Vandenbroucke *et al*, 2007).

## 6. Evidence for autonomic dysregulation in the irritable bowel syndrome (2002)

**Authors:** Vishal Gupta, David Sheffield, G. Nicholas Verne

**Aim:** To evaluate differences between resting blood pressure and heart rate between IBS-patients and HC. The aim was also to examine if there is a correlation between resting heart rate and/or blood pressure and ratings of pain intensity/unpleasantness in response to balloon distension of rectum and cutaneous thermal heat.

**Methods:** In 20 IBS-patients and 23 HC blood pressure and heart rate were measured. Pain intensity and unpleasantness to visceral and cutaneous stimuli were measured using rectal distension of a balloon for 30 seconds with a 60 seconds rest between inflations and immersion of the foot in a hot circulating water bath at temperatures of 47°C for 20 sec each with a 5-min rest between each stimulus. The subjects were blinded to stimulus intensity by presenting the various intensities of visceral and cutaneous stimuli in random order. The visceral and cutaneous stimuli were presented in random order and counterbalanced across all subjects. The examiner who administered the psychologic tests and the visceral/cutaneous pain testing was blinded to the specific group (control versus IBS) to which each subject belonged. Pain and unpleasentness were graded on a mechanical visual analog scale.

**Results:** Pain intensity and unpleasantness was rated significantly higher in IBS patients than HC (P<0,0001). IBS-patients had higher mean resting heart rate than HC. There were no relationships in controls between blood pressure, visceral and cutaneus pain but in IBS-patients blood pressure was significantly inversely associated with visceral pain and only weakly and positively associated with cutaneous pain.

**Conclusion:** The findings in this study is evidence suggestive of a mechanism of autonomic dysregulation in IBS patients compared to controls. It indicates that

there ia a higher activity in SNS than PSNS i IBS-patients that are diaorrhea-predominant (Gupta *et al,* 2002).

STROBE statements failed to be achieved: 1a, 5, 12c, 13a,b, 14a,b, 19, 22 (Vandenbroucke *et al*, 2007).

## 7. Evidence for Autonomic Nervous System Imbalance in Women with Irritable Bowel Syndrome (1998)

**Authors:** Margaret Heitkemper, Robert L. Burr, Monica Jarrett, Vicky Hertig, Mary Kathleen Lustyk, Eleanor F. Bond.

**Aim:** To evaluate ANS activity by describing and comparing frequency indices of HRV across 24 hr in women with and without a diagnosis of IBS.

**Methods:** 25 women with IBS and 15 HC were interviewed and followed during one menstrual cycle with a symptom diary, and during mid-luteal phase they wore a Holter 24-hr electrocardiograph monitor to measure HRV.

**Results:** The IBS group showed significantly lower vagal tone compared to HC, this pattern manifestated as a flattened 24hr pattern of HRV with significantly lower levels of vagal tone during sleep.

**Conclusion:** Women IBS-patients has a systemic sympathovagal imbalance that is shifted to a higher sympathetic activity and a lower parasympathetic activity (Heitkemper *et al,* 1998).

STROBE statements failed to be achieved: 1a, 13b, 14b (Vandenbroucke *et al*, 2007).

## 8. Sex specific alterations in autonomic function among patients with irritable bowel syndrome (2005)

**Authors:** K Tillisch, E A Mayer, J S Labus, J Stains, L Chang, B D Naliboff

**Aim:** To test differences in ANS function during rest and with an acute visceral stressor (balloon distension) between IBS patients and healthy control and also examine the role of subject sex on these responses.

**Methods:** Heart rate variability measures of peak power ratio (PPR) and peak power high frequency (PPHF) were analysed to assess sympathetic balance and parasympathetic response, respectively in 46 IBS-patients and 16 HC during a sigmoid balloon distension. Peripheral sympathetic response was measured by skin conductance. Baseline data of ANS were also evaluated from 130 IBS-patients and 55 HC.

**Results:** IBS males were showing a significantly higher PPR sympathetic ratio compared with IBS females ($p<0.001$), control females ($p = 0.003$), and control males ($p = 0.026$). This study also demonstrated evidence of higher SNS activity and lower cardiovagal activity in the IBS-patient group. Within the IBS population there were significant sex differences, with greater SNS activity and lower PNS activity in males compared with females. IBS patients showed a greater skin conductance response to visceral distension than controls. IBS patients had higher PPR and lower PPHF across conditions. Male IBS patients had higher skin conductance and PPR than females and lower PPHF.

**Conclusion:** IBS patients have altered autonomic responsiveness to a visceral stressor, decreased parasympathetic tone and increased sympathetic activity with altered ANS responsiveness are prominent in IBS male patients, but not IBS females (Tillisch *et al,* 2005).

STROBE statements failed to be achieved: 1a, 5, 9, 10, 14, 19 (Vandenbroucke *et al*, 2007).

**Summary of results:** All 8 articles showed that there are dysfunctions of the ANS per se. But the desribed most affected part of the ANS differed between the studies. 6 studys showed an increase of the activity in the SNS and study no.4 showed an increase in the PSNS whereas study no.5 showed an alteration in the ANS activity without being able to define whether SNS or PSNS activity were higher.

# 6 Discussion

## 6.1 Discussion of methodology

This is a systematic literature overview, implicating analysis of 8 studys created from 1998 and forward, three of the articles analysed were produced in the last four years and one focus of this study was to use research done as up to date as possible to reflect the knowledge of today. The keywords used in the search of articles were Meshterms and in combination they should cover the most relevant research in the database regarding the area of interest, despite this four of the articles that were analysed were taken from referenses of other articles but nevertheless they existed in the PubMed database without appearing in the keywordsearch (Higgins *et* Green, 2008). With this knowledge perhaps more interesting articles would have been found if more keywords would have been used but 8 articles were considered to be enough by the author. Maybe if the selection of articles of interest would have been larger, the author would have selected more studies performed more recently which might had made this thesis a bit more up to date. The STROBE statement checklist of items that should be included in a case-control study was used as a help to analyse the eight chosen articles, this is the first time the author uses this checklist and because of this fact it could be seen as a possible threat to the validity of this study (Jüni *et al,* 2001). The amount of research done on IBS is practically infinite and it could seem inadequate to search as few databases as the author did in this study but the amount of articles found were considered to be enough to give a representative picture of where the research has come today for a study of this size. The databases used are worldleading in this field and the main part of important scientific articles written in the subject relating to this study could be supposed to be found there (Higgins *et* Green, 2008). The articles used are all peer-reviewed studys from wellknown scientific journals which ensures a certain degree of quality hence it is a strenght of this study however the level of evidence of this thesis is low because it is not reviewed by different indenpendent experts like the peer-reviewed studies are (Higgins *et* Green, 2008).

## 6.2 Discussion of results

The discussion of results will start initially with a discussion of the results of the analysed studies and the question of this thesis: “Is there evidence for a dysfunction of the autonomic nervous system in patients with irritable bowel syndrome compared to healthy controls” and later articles that were analysed will be discussed individually and then continue with a summary of these results related to the main question of this study, osteopathic considerations and benefits/limitations of this study.

The results of all 8 studies showed some type of abnormal function of the ANS compared to HC which, in itself, answers the main question that there actually exists a dysfunction of the autonomic nervous system in IBS-patients. Different methodological prerequisities creates possible selection bias like gender, both mixed groups and only women or men existed (Jüni *et al,* 2001). How the studys decided the sample size is of importance since a small sample size dont have to mean that it is a low quality study but only study no. 5 and 7 discussed this which is a possible methodological limitation (Higgins *et* Green, 2008). It is impossible to randomize participants since the IBS-group must have the disease and the HC must be healthy but blinding of assessors were only used in study no.6 but could strenghten the quality of the other studies if being used there as well (Jüni *et al,* 2001).

**Study 1:** Strenghts of this study is that the IBS-group consists of a fairly even mix of both men (n=12) and women (n=18), the study size of 30 patients seems ok but is not discussed and the p-value is ($p<0.05$) which indicates that the statistical significance could be better (Jüni *et al*, 2001). Only constipation-predominant patients were included, since diarrhoea and constipation as well as the ones alternating between theese seems to have significantly different results when testing the ANS this is probably easier to get consistent measurements from (Aggarwal *et al,* 1994). Many different tests to evaluate the ANS were used which decreases the risk of systematic errors. On the negative side there were no information about the social status of the participants and this confounder can also affect the results and increase the risk of selection bias (Camilleri *et al*, 2002). Ten STROBE statements were not fulfilled and it was not accounted for attrition bias due to missing data,

possible efforts to eliminate other potential bias as well as limitations of the study were not discussed sufficiently. Despite these negative aspects the overall impression of the study is good. There were no information regarding funding of this study which in worst case could account for funding bias (Vandenbroucke *et al,* 2007).

**Study 2:** This study is interesting because it compares 10 fibromyalgia patients and 13 IBS patients but the size of those groups and the 10 HC would preferably be larger to eliminate selection bias because of the different nature of these diseases (Vandenbroucke *et al,* 2007). The IBS-patients had different attributes regarding constipation, diaorrhea and alternating which may increase the dispersion of the autonomic measurements in this group (Aggarwal *et al,* 1994). Baseline ANS activity was recorded for 2 minutes at the beginning of every session while participants were instructed to relax and this may create systematic biases because of anxiety of patients that soon after this measurement will be exposed to pain, this bias may also have different effect between groups because of different ANS responding and these baseline data would probably have been better to record on a day different from the paintesting day. Nine STROBE statements were not fulfilled and they included that missing data were not adressed, participants psychological profile were not evaluated and the discussion of potential biases were not satisfying. There were no information regarding funding of this study either.

**Study 3:** This study is very thorough and well done. Only three STROBE statements were not achieved and the most important of them was that the article didn´t declare from were it was funded. IBS-attribute of the patients were not reported which is a negative aspect because of the increasing risc of selection bias (Jüni *et al,* 2001). Positive sides of this study was that considerations were taken to participants social and psychological status, statistical tests to detect errors due to multiple dependent variables were performed and a large studygroup was used (106 IBS-patients). In conclusion, the authors of this study shows clear results and has tried to eliminate bias as much as possible.

**Study 4:** This study differs in results from the others used in this thesis when stating that IBS-patients shows increased PSNS activity and decreased SNS activity. The menstrual cycle phases of women in the study were not controlled for or assessed and this a source of possible bias, 4 out of 14 IBS-patients in a fairly small IBS group were taking medication for their IBS symptoms and the group was a mixture of diarrhoea, constipation and alternating IBS, all of theese is possible causes for bias (Aggarwal *et al,* 1994). Unfortunately participants social and psychological status were not considered. Baseline physiologic measures were recorded for 2 minutes before the paintesting procedure and as stated in study 2 this might create systematic bias. HRV were measured and in addition to this, fluctuations in skin conductance, were also used which is a strength of this study. The foot immersion in 7degrees cold water for 120 seconds can possibly be to intense and longlasting hence supress groupdifferences and fail to give reliable results. Five STROBE statements were the study unsuccesful to reach which is quite good but the overallimpression is that there are many uncertain factors which may lead to different types of bias and possibly explain the contradictory results compared to the other articles analysed.

**Study 5:** In this study they have a different angle in their intervention, they wanted to examine the role of neuronal histamine in the ANS by administrate chlorphenamine and measure ANS responses differences between subjects and controls. This study was included in the thesis because of the close relationship between IBS and fibromyalgia and the author found it interesting to use because of this. The number of participants would preferably have been larger and the IBS-group consisted of a mixture of all three attributes which probably will have greater probability to create selection bias the smaller the group is (Vandenbroucke *et al,* 2007). The authors failed to show any correlation between hypnotic suggestions or visceral stimulation and ANS responses and the other outcomes were not as clear as one would have wished. Five STROBE statements were not fulfilled and the organization of the study is good. Possible bias are discussed and the funding of the study is declared. The overall impression is good but the clarity of the results and the interpretation of them is questionable.

**Study 6:** A studygroup of 20 IBS-patients is ok but it would preferably have been larger since the fact that there were 18 women and 2 men might contribute to selection bias and the dividing between men and women should been more even since sexdifferences seems to affect the autonomic responses of IBS-patients, but in favor of this study is that all IBS-patients were diarrhoea predominant (Tillisch *et al,* 2005). There were blinding of both subjects and examiner to avoid interviewer bias and a psychologic evaluation of IBS-patients was performed which is an advantage (Higgins *et* Green, 2008). The analyze according to STROBE statements showed that there were no information about social status or how the subjects were recruited or how missing data were handled, limitations and funding of the study was not either clarified. These weaknesses could possibly produce confounding, attrition bias and funding bias however the methodology as well as the discussion part of the study is wellwritten and informative which makes some of these biases less likely (Vandenbroucke *et al,* 2007). To sum up this study it has some deficiencies regarding the background data of the studygroup and how it was selected plus poor discussion of limitations of this study but other than that it is clear and shows distinct results and is of good quality.

**Study 7:** This study contains a very thorough explanation of the set-up of the studygroup which is good but stoolpatterns of the participants is a mix of diarrhoea, constipation and alternating which, as stated before, can possibly produce selection bias but this is carefully considered in the discussion part (Aggarwal *et al,* 1994). 25 IBS-patients in the studygroup is ok but 7 of them where taking antidepressive medications which, according to the author of the study, did not affect HRV results but still this should probably be considered as a potential source of detection bias. The study contains good explanations of efforts to reduce different bias and errors in the measuring of HRV and the statistical analyses of results. Results are presented in a clear and obvious manner and the discussion part elaborates different concepts of ANS and HRV relating to this study. Only 3 STROBE statements were failed to be achieved which is a very good result and they mainly were about the loss of explanation about what was done with potential missing data, if this occured, of the subjects that started but never carried

out the whole study or did not present with complete data hence this could produce attrition bias (Jüni *et al,* 2001). To conclude, this is one of the analyzed articles with the highest quality however it is also the oldest one which should be taken in consideration bearing in mind that much knowledge about IBS has been revealed since this article was produced in 1998.

**Study 8:** This study contains a large IBS-group of 130 patients which is satisfying but there is no information about when the baseline data were measured, if it was just before the test began or the day before remains uncertain. There were 64 males and 63 females in the IBS group and the fact that there were all different IBS-attributes (diarrhoea, constipation, alternating) present were taken in consideration in the statistical analyses and this, together with the high number of participants, are important strenghts of this study (Jüni *et al,* 2001). The STROBE statement analyzes revealed 6 criteria that were not reached, mainly regarding the information about the participants, efforts to eliminate different bias and discussion of limitations of the study. To conclude the analyze of this study it is of high quality and the results seems to be reliable even if there are some gaps in the methodspart regarding the information about the participants.

**Summary:** All articles that were analysed are casecontrol studies, peer reviewed and published in well known journals and analysed by the STROBE statement criteria which all articles passed more or less good and this strengthens the quality of the studies (Vandenbroucke *et al*, 2007). Remarkably none of the studys analysed fulfilled the STROBE statement criteria 1a and told the reader which type of study it was, but his does not really affect the quality of the study. The main general problems according to the STROBE criteria is lack of complete information about the participants and their etnicity, social status, psychological status etc. and also information about how missing data were handled and efforts to eliminate potential bias. Only three of the analysed articles revealed information about funding and this could be important since pharmaceutical companies often supports studies with funding and if, for example, they developed a drug that lowers SNS acti-

vity in constipation-prone IBS-patients the risk of funding bias in a study that evaluates ANS activity in these patients possibly is larger than if the funding came from a company not related to this drug (Vandenbroucke *et al*, 2007). Different results and conclusions of the articles are probably due to methodological differenses in which parameters related to the ANS that were measured, for example HRV, GSR, MAP, blood pressure, Plasma adrenalin, noradrenalin, insulin, ghrelin and cholecystokinin, plasma catecholamines and histamin etc. Many studies uses HRV as a measuring tool of ANS activity and the validity of this is reliable but still debatable (Mazurak *et al,* 2012). There were also differences in intervention like electrical stimulation or balloon inflation in the rectum, administration of chlorphenamine, immersion of the arm or foot in water with slightly or largely (hot or cold) different temperatures, that can cause different results. Another big issue is that the different attributes of IBS-patients seems to show different patterns of ANS dysfunction. One study reported that those patients with diarrhea-prone IBS exhibited significantly higher levels of SNS activity and constipation-prone patients exhibited significantly lower levels of PSNS activity relative to controls (Aggarwal *et al,* 1994). It seems difficult to decide if there is an increase of SNS activity or a decrease of PSNS activity but the fact that there exists a dysfunction of the ANS seems practically certain, the level of the dysfunction, meaning central or peripheral, is still up for debate and probably differs from case to case. The importance of this dysfunction is, despite much research in the area, not obvious but it is very likely a big factor and it is still difficult to state if it is a cause of the problem or a consequence of the condition. Many different treatments of IBS are available but since IBS is a multifactorial condition with a large spectrum of symptoms and intensities, different patients will probably benefit from different kinds of treatments and here osteopathy should be able to live up to it´s principles of adressing and treating the whole body (Chila *et al,* 2011). Osteopaths have a big variety of treatment techniques and approaches that can be used to meet a problem in the most appropriate way, which should be optimal for conditions like IBS. In the osteopathic treatment of a patient with IBS there are usually many coexisting muskuloskeletal defects found, the osteopath tries to identify locations of the most primary disturbing structures and consequently affect, for example the ANS, through the idea that structure and function are reciprocally related and, according to Kuchera, the specific osteopathic manipulative techniques for treating

IBS are designed to balance the SNS and PSNS, relieve venous and lymphatic congestion in the intestinal tract and to remove chronic joint somatic dysfunctions which play a role in perpetuating detrimental facilitated cord segments (Kuchera *et* Kuchera, 1994). That osteopathy can affect the ANS is something that probably is obvious to most osteopaths with a few years of experience but this knowledge has been largely observational and based on patient outcomes such as improvement in pain scales, range of motion, and other empiric measures. There are some evidence from scientific studies showing that osteopathic manipulative treatment has significant effect on the ANS activity but many more studies with higher quality and other methodological preferences are desirable (Henley *et al,* 2008). If the primary ANS dysfunction lies more centrally in one patient, possibly cranial techniques could be the main choice of treatment techniques but if the primary ANS dysfunction is located more peripherally in another patient, that patient might benefit more from visceral techniques and high velocity thrusts in related joints of viscerosomatic reflexes. As stated earlier, relating to the title of this thesis, it is difficult to say with certainty exactly how much the ANS is involved in the generation and maintenance of IBS but it feels safe to say that it plays a major part and is an important factor to include in the treatment of IBS, however IBS is depending on so many factors, both psychological factors in the present and in the past, diet, lifestyle, genetic factors, bodytype, social factors etc. and because of this, IBS-patiens would probably get the best results by combining treatment with changes in lifestyle, diet, reduce stress etc. The possibilities to find a single cure for IBS seems very unlikely because of it´s multifactorial origin but the better the pathophysiology is understood the better the treatments will probably get.

# 7 Conclusion

One can say with high validity that there exists a dysfunction of the autonomic nervous system in IBS-patients compared to healthy controls. The nature of the dysfunction tends to point towards increased sympathetic activity and decreased parasympathetic activity. However larger studygroups and more uniform methodology is necessary to get more consistent results. To be able to refine the methodology in future studies groups with IBS-patients needs to be divided in subgroups depending on the stoolpattern, psychological status and gender.

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# 9 Appendix

## 9.1 STROBE Statement

STROBE Statement—Checklist of items that should be included in reports of ***case-control studies***

| | Item No | Recommendation |
|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses |
| **Methods** | | |
| Study design | 4 | Present key elements of study design early in the paper |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls |
| | | (*b*) For matched studies, give matching criteria and the number of controls per case |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| Bias | 9 | Describe any efforts to address potential sources of bias |
| Study size | 10 | Explain how the study size was arrived at |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |

| | | |
|---|---|---|
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding |
| | | (*b*) Describe any methods used to examine subgroups and interactions |
| | | (*c*) Explain how missing data were addressed |
| | | (*d*) If applicable, explain how matching of cases and controls was addressed |
| | | (*e*) Describe any sensitivity analyses |
| **Results** | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
| | | (b) Give reasons for non-participation at each stage |
| | | (c) Consider use of a flow diagram |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders |
| | | (b) Indicate number of participants with missing data for each variable of interest |
| Outcome data | 15* | Report numbers in each exposure category, or summary measures of exposure |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
| | | (*b*) Report category boundaries when continuous variables were categorized |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |

| | | |
|---|---|---|
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |
| **Discussion** | | |
| Key results | 18 | Summarise key results with reference to study objectives |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results |
| **Other information** | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

*Give information separately for cases and controls.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

## 10 Declaration of Conformity

I hereby declare on oath, that I have written this thesis independently and that I have only used the sources and aids above mentioned. I have neither submitted this nor any other work elsewhere. Moreover, there is no conflict of interest between this work and other people and/or institutions.

Signature