A capital role for the brain's insula in the diverse fibromyalgia-associated symptoms

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Sources of support

J.V.O. holds a post-doctoral research fellowship funded by the Research Foundation – Flanders (FWO) [12L5619N and 12L5616N].

Abstract

Unexplained yet persisting general and widespread non-articular musculoskeletal pain and the associated complaints, known as fibromyalgia (FM), is a common disorder with major social and economic impact. We postulate that in FM dysregulation of neurotransmitter balances at the brain's insula not only leads to aberrant pain processing but could also govern other associated symptoms. Symptoms might arise from central nervous system dysregulation mediated through an imbalance between the excitatory neurotransmitter glutamate and the inhibitory transmitter gamma-amino butyric acid. The insula could also have a leading role in the dysregulation of heart rate and blood pressure, bladder and bowel symptoms, and anxiety and sleep disturbances which are experienced by many FM patients. The presented hypothesis explains how the diverse FM-associated symptoms could be linked, and puts the brain's insula forward as a possible therapeutic target to be further explored for FM.

Introduction

Patients diagnosed with fibromyalgia (FM) present with persisting unexplained general and widespread bilateral muscular and joint pains [1]. Diagnostic evaluation includes a thorough history and physical examination along with laboratory testing. Diagnostic criteria are constantly being fine-tuned and scrutinized, as well as the description of other syndromes the condition associates with [2, 3] (Figure 1). To evaluate the patient's subjective pain perception, instruments have been provided by the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-APS Pain Taxonomy [4], and the American College of Rheumatology has drawn up criteria for the diagnosis and determination of symptom severity [5].The estimated overall prevalence of FM in Europe is 4.7% when chronic widespread pain is considered, and 2.9% when combined pain and fatigue criteria are used [6]. In addition to pain and fatigue, abnormal functioning of the autonomic nervous system may cause delayed, inappropriate or exaggerated responses to external or internal stimuli. A validated method to recognize this dysautonomia is the composite autonomic symptom score (COMPASS) questionnaire, and FM patients score significantly higher in all COMPASS domains. Most FM patients report orthostatic, digestive, sleep, sudomotor, or mucosal dysfunction, and COMPASS scores significantly correlate with FM severity [7].

Despite overt myalgia, and stiffness and tenderness of the muscles, tendons and joints, the tissues involved do not display demonstrable histological degradation or damage. The key to disease etiology therefore appears to lie in pain perception and processing, which are affected by autonomic and neuro-endocrine processes. The insula, a brain region that lies deeply buried inside the lateral sulcus, is an influencer of human thoughts and behaviors, and a key processor of pain signals [8]. Four functionally distinct regions of the insula are activated in response to a wide variety of stimuli, i.e: 1) a sensorimotor region located in the mid-posterior insula; 2) a central-olfactogustatory region; 3) a socio-emotional region in the anterior-ventral insula; and 4) a cognitive anterior-dorsal region [9]. The posterior insula is thought to analyze the primary sensory sensation of pain stimuli, while the

anterior insula has been associated with processing of subjective pain-associated feelings [10]. Dynamic alterations in pain sensitivity have been associated with changes to the insular brain anatomy and connectivity [11-12].

We here postulate that the brain's insular region might be key not only to persistent pain in FM, but also to the diverse other associated symptoms that patients experience, as an essential component of underlying central (autonomic) deregulation. More specifically, the imbalance found in the excitatory and inhibitory neurotransmitters in this region could provide an explanation for chronic pain as a main symptom, as well as for common additional symptoms in FM.

Evidence linking the brain insula to the diverse FM-associated symptoms

Pain perception and processing

Within the insular cortex, the balance between the excitatory neurotransmitter **glutamate (Glu) and gamma-amino butyric acid (GABA)**, the main inhibitory transmitter of the central nervous system, shapes pain perception and modulates pain tolerance. The Glu/GABA–glutamine cycle is a metabolic pathway that describes the release of Glu or GABA from neurons which are then taken up into glial cells. In return, glial cells release glutamine to be taken up into neurons for use as a precursor to the synthesis of Glu or GABA [13]. Prolonged exposure to agonists drives GABA receptors into a refractory or desensitized state. This process of receptor desensitization is an important feedback mechanism to decrease the body's sensitivity to a stimulus [14-15]. The levels of the excitatory neurotransmitter Glu across pain-related brain regions positively correlate with individual pain sensitivity [16]. In the posterior insula of healthy volunteers, pinprick-induced pain intensity correlates inversely with GABA levels, and positively with Glu levels [17]. Mean Glu/glutamine levels are significantly higher and mean GABA levels significantly lower within the posterior insula of patients with diabetic neuropathy compared to healthy controls [18]. Evidence also supports an involvement of imbalanced excitatory and inhibitory neurotransmitters in FM. FM patients had

significantly higher levels of Glu and combined Glu and glutamine within the right posterior insula as compared to controls, which was associated with lower pressure pain thresholds [19]. Anomalies of GABA and Glu turn-over may thus play an important role in FM.

Magnetic resonance imaging studies have also picked up altered **functional connectivity** between areas of the brain involved in pain processing and interpretation in FM patients compared to healthy controls. The brain regions concerned included the dorsolateral prefrontal cortex, anterior cingulate, amygdala, hippocampus, and the insula [20]. Possibly, alterations to the descending pain modulatory network play an important role in sustained pain in FM patients. FM is commonly comorbid in migraine patients [21], a chronic pain disorder which has been shown to associate with altered insular function [22].

Cardiovascular symptoms

Cortical regions that include the medial prefrontal cortex [23], anterior cingulate cortex [24] and the insular cortex [25] are involved in the maintenance and regulation of heart rate and blood pressure [26]. Damage to the insular cortex has been associated with arrhythmia, diurnal blood pressure variation disruption and myocardial injury [27]. In addition, a 20% higher prevalence of mitral valve prolapse has been reported in FM subjects than among the general population [28].

Analysis of electrocardiograms of FM patients show fluctuations of **heart rate** and oscillation in the interval between consecutive heartbeats, characteristics suggestive of an abnormal sympathovagal balance [29]. Based on a systematic review it indeed appears that heart rate variability and autonomic activity are altered in FM patients, with lower heart rate variability and a dominance of sympathetic activity and reduced reactivity of the autonomic nervous system to stressors [30]. Postural tachycardia syndrome, an abnormal increase in heart rate that occurs after sitting up or standing, is commonly reported in FM [29]], and patients display differential cardiac responses to exercise. In healthy subjects, exercise is accompanied with dynamic adaptive changes which result in an increased blood flow and redistribution of the blood, aimed to provide the working muscle with

the energy it necessitates. The heart rate increases immediately at the onset of activity as a result of parasympathetic withdrawal [31] and, as exercise continues, heart rate further increases due to activation of the sympathetic nervous system, reflected by an increased Low Frequency/High Frequency (LF/HF) ratio [32]. Parasympathetic withdrawal and sympathetic excitation during exercise reverses these effects during recovery [31]]. It is likely that FM patients have altered autonomic responsiveness to physiological stress reflected by lower sympathoadrenal activity during acute bouts of exercise [33-34]. In a cohort of female patients, reduced sympathetic and increased parasympathetic regulation of heart rate after acute resistance exercise has been reported [35]. A study by Del Paso et al. [36] investigated heart rate variability and LF/HF ratio in FM patients subjected to a mental stress task, and found it was reduced during the task, while it increased during recovery, in contrast to the control group where the LF/HF ratio remained relatively constant across the whole procedure. Reduced heart rate variability as observed in FM might, however, also be related to reduced physical activity in patients. A study reported reduced physically activity in FM patients compared to healthy controls. Physical activity levels were not predictive of pain, but were significantly related to depressed mood [37].

Bladder and bowel symptoms

The afferent signals that bring a full bladder to our conscious attention motivate appropriate bladder emptying. Processing of bladder signals is exerted by a network of brain regions, which includes the thalamus and prefrontal cortex, but also the brain's insula [38]. FM patients commonly complain of urinary symptoms such as **increased frequency or urgency**, and **pelvic distress**. Women diagnosed with FM have 50% greater pelvic floor symptoms compared with age-matched controls [39] and urinary symptoms are associated with more severe FM phenotypes [40].

Communication between the brain and gut is complex and involves multiple systems including the brain cortex, hypothalamus, and pituitary and adrenal glands. These structures are closely linked either by the peripheral nervous system or through neurohumoral stimuli. While the enteric nervous

system participates to the local coordination of gastrointestinal functions, Glu is also involved in the regulation of the brain-gut communication, through its regulation of a bi-directional connection pathway. The neurotransmitter conveys information to and from the gut to the brain, sending the signals to appropriately control gut secretion and motility. Inappropriate control of this system can lead to gastroesophageal reflux, gastric acid hypersecretion and irritable bowel syndrome. The presence of the latter condition is strongly associated with an increased thickness of the posterior insula [41]. Functional disorders of the gastrointestinal tract that are characterized by **chronic abdominal pain or discomfort** are highly associated with FM [42], with an overall increased incidence in patients [43]. In patients with irritable bowel syndrome, FM is present in 20%, displaying a significant association with the severity of the intestinal disorder [44].

Anxiety and depression

The control one perceives over aversive events is an important factor influencing psychological wellbeing and requiring complex construction linkage between cognitive and emotional experiences. In these processes, the insular cortex appears critically involved [45], and evidence accumulates of altered insular activation in individuals with dysregulated mood or anxiety [46]. Subjects with high trait anxiety show enhanced activation in the anterior insula during the emotional processing of aversive images [47]. The right anterior insula appears critically involved in depression, with patients displaying strong amygdaloid connection and reduced connection to the dorsolateral prefrontal cortex [48]. An association of depression severity with disturbed hippocampal function and impaired connectivity with other brain regions, has been proposed.

Psychiatric comorbidities, especially depression and anxiety, are common in chronic pain conditions. A large study examining disease phenotype in 115 FM patients reported more than 30% experienced **anxiety and/or mood disorders** [49]. Stressful life events may trigger FM or worsen its symptoms and can arise as a result of apprehension about chronic pain or be triggered by prolonged fatigue.

However, clinical depression and anxiety have also been documented to precede FM and to contribute to disease development [50, 51].

Fatigue and disordered sleep

A disabling unexplained lack of energy, termed fatigue, is highly common and persistent in FM [52]. Analysis of patient-reported symptoms shows FM-associated **fatigue** to be physical, emotional as well as cognitive in nature [53]. Fatigue appears, in part, to be related to unrefreshing sleep or poor sleep quality. Parallel mechanisms of homeostatic and circadian regulation controlled by the hypothalamus and the suprachiasmatic nucleus respectively control a person's sleep/wake cycles. Sleep quality perceived by individuals, however, relates to emotional empathic responses generated through increased neural activation of a specific area within the insular cortex. FM patients report **decreased sleep quality**, and patients experience worsening of pain symptoms after poor sleep [54]. Abnormalities in melatonin and cortisol, two hormones of which secretion is strongly influenced by the circadian pacemaker, have been reported in female FM patients [55], yet a study evaluating the circadian amplitude or phase of rhythms of melatonin, cortisol, and core body temperature failed to reveal significant differences with healthy controls [56]. Polysomnography did demonstrate that FM patients exhibit reduced short-wave sleep and abnormal α-rhythms, suggestive of wakefulness during non-rapid eye movement sleep [57]. Occurrence of daytime hypersomnolence in FM patients is linked to more severe overall symptoms [58]. Fatigue might be linked to the brain's insular function. In patients diagnosed with rheumatoid arthritis, pain as well as abnormal fatigue appear to be important symptoms, and imaging reveals underlying functional and structural changes to the brain, with increased connectivity within the left insular region [59].

Obstructive sleep apnea arises when the insular cortex responds inappropriately to autonomic challenges, which is suggestive for a neural reorganization. Left and right anterior insular cortices show lower GABA and higher Glu in patients with obstructive sleep apnea than in healthy subjects [60]. **Obstructive sleep apnea** is prevalent in FM and is present in some 45% of patients [61]. Patients

frequently report dyspnea, a process to which the insular functional network participates [62]. In dyspnea induced by administering isoproterenol, the right mid-insular cortex is a centrally involved region [63]. **Non exercise-induced dyspnea** is common in FM [64], and patients more often report increased shortness of breath than healthy controls [65].

Small Fiber Pathology

Reduction of intra-epidermal nerve fiber density, termed small fiber neuropathy, is caused by damage to peripheral nerves and associates with a variety of diseases. The condition usually presents with pain and autonomic dysfunction [66]. It could represent a functional reorganization of the peripheral nervous system in response to hyperactivity of the central nervous system, in an attempt to regain homeostasis by reducing the afferent sensory input [67] . An experimental study in Sprague Dawley rats suggested that increased insular Glu is associated with a reduction in intra-epidermal nerve fiber density [67]], thus implying that a central neurotransmitter defect may contribute to small fiber pathology. The use of an inhibitor of the transport of Glu in the insula of rats for 6 weeks resulted in an increased sensitivity to pain with likeness to the symptomatology of FM patients. The findings that small fiber pathology and the increased Glu in the insula are linked, makes it worthwhile to highlight the track in which the insula might be the main region in the brain in FM pathology.

A recent meta-analysis reported a high prevalence of **small fiber pathology (SFP)**, with 49% of FM patients having a structural abnormality of the small nerve fibers (based on a stringent literature search which retained eight studies representing data from 222 patients in total) and found an average 45% prevalence of SFP in FM patients when a skin biopsy was evaluated, and 59% of FM patients when confocal corneal microscopy was used [68]. SFP in FM needs to be distinguished from small fiber neuropathy, as the underlying mechanisms causing pathology in small fibers remains to be elucidated and the clinical phenotype of FM is distinct [69]. It needs to be determined whether SFP is a consequence or a true cause of the symptoms that can be observed in FM, and how it relates to the altered central nervous system processes that are obvious in FM.

Treating FM through pharmacological modulation of neurotransmitter metabolism

Pharmacological treatment of FM is currently under extensive development. It has been established that modulation of Glu receptors has potential for therapeutic utility in several categories of persistent pain. The major Glu receptor subtypes at glutamatergic synapses are subdivided into ionotropic (including N-methyl-d-aspartate (NMDA)) and metabotropic Glu receptors. NMDA receptors are concentrated at postsynaptic sites on dendrites and are critical for the development of the central nervous system and the processes of learning and memory. Metabotropic Glu receptors are widely distributed G-protein coupled receptors that modulate neuronal activity.

NMDA receptor activity is increased in FM, hence it is a target for therapeutic intervention. Activation of the NMDA receptor results in increased sensitivity to sensory information processing, yet the overall benefit of current **NMDA receptor antagonists** in FM patients appears modest [70]. Ketamine appears a potent NMDA receptor antagonist drug, yet can be associated with a wide variety of adverse effects. In a cohort of 60 patients with complex regional pain syndrome type 1, ketamine led to significant pain relief without functional improvements, and with psychomimetic side effects being acceptable to most patients [71]. Other NMDA receptor antagonists with effects across a variety of neurological and psychiatric disorders have potential beneficial effects toward pain syndromes, including dextromethorphan [72] and memantine [73]. A novel class antagonist termed NYX-2925 has been tested in a phase I study showing that the drug is safe and well-tolerated in healthy volunteers [74]. In a first in-human phase 2 study in patients with painful diabetic peripheral neuropathy, NYX-2925 showed numerical improvement which was, however, not statistically significant. Study results are, nonetheless, supportive of further clinical development, and suggest longer treatment than the evaluated four weeks may result in more extensive improvement [75].

Another possible strategy for pain relief is the systemic administration of **antagonists of metabotropic Glu receptors**, the G protein-coupled receptors responsible for the slow

neuromodulatory response to Glu. Accumulating evidence indicates that these receptors are significantly involved in psychiatric conditions [76], making that pharmacotherapy developed for treating psychiatric disorders can have beneficial effects on FM patients. Major depression commonly co-occurs in 20 to 40% of FM patients [77].

Alternative use of **anti-epileptics** for pain relief has also been proposed. Gabapentinoid drugs (derivates of GABA), are now often prescribed to relieve pain. Gabapentin and pregabalin have been shown efficacious for treating painful diabetic neuropathy and postherpetic neuralgia [78], and the latter drug has been approved by the U.S. Food and Drug Administration (FDA) for treatment of FM. Two meta-analyses assessing the efficacy of pregabalin by analyzing five FM trials concluded that pregabalin treatment significantly reduced pain, improved sleep, and positively influenced health-related quality of life in patients [79, 80]. The precise activity of pregabalin remains elusive, but it is apparent that it inhibits presynaptic excitatory neurotransmitter release by blocking α2δ calcium channels, thereby probably decreasing the release of Glu into the synapse. Pregabalin reduces combined Glu/glutamine levels within the posterior insula of FM patients [81].

Non-pharmacological treatment for FM

Brain stimulation has been under consideration for FM patients for some time but, although repeatedly reported in the literature to relieve pain, its potential remains contested. The arsenal of therapeutic brain stimulation techniques does, however, expand steadily, and the prospect of non-invasive transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) to treat pain disorders has arisen. The first generates electrical currents in the targeted brain area using polarity changes in magnetic fields created by a magnetic coil which is positioned just above the scalp, in the latter stimulation is achieved via electrodes in direct contact with the scalp producing a subthreshold change in neuronal membrane potentials. Anodal stimulation usually results in cortical excitability, whereas cathodal stimulation usually results in cortical inhibition [82]. Nevertheless, repetitive TMS (rTMS) target to primary motor cortex (M1) may have some beneficial effects for

neuropathic pain [83] and FM [84]. A meta-analysis showed significant favorable effects [85], suggesting a better analgesic efficacy of M1 stimulation and a better antidepressant effect after high frequency rTMS of the dorsolateral prefrontal cortex (DLPFC). Because of its implication in the experience of pain, insular cortex stimulation could be an alternative target region to stimulate [86]. Preliminary studies showed that continuous theta burst stimulation [87] and rTMS [88] over the insular cortex resulted in a reduction of the perception of acute cutaneous pain. However, other stimulation protocols targeting the insula failed to be effective in chronic central neuropathic pain [89]. Consequently, concerning FM and other dysfunctional chronic pain syndromes, no recommendation was made for the use of rTMS (left M1 and left DLPFC) in these conditions [90]. On the other hand, Lefaucheur et al. [91] recommended a probable efficacy regarding the analgesic effect of anodal tDCS of the left M1 in FM. However, given the potential concomitant effects on depression and anxiety, the clinical relevance of the intensity of pain relief is still under debate. It must also be noted that for rTMS and tDCS only acute effects were investigated, leaving the long-term clinical outcomes and effects on neurocardiac regulation [92] unexplored.

Invasive deep brain stimulation requires neurosurgical implantation of bipolar electrodes attached to a permanently implanted pulse generator [93]. In an experimental rat model of peripheral neuropathy, electrical stimulation of the insular cortex reversed mechanical hypersensitivity in the paw through modulation of the functionality of opioid and cannabinoid systems in the periaqueductal gray matter pain circuitry [94]. With this highly focal technique, deeper brain regions can be reached. Ventral striatum/anterior limb of the internal capsule stimulation in 10 patients with poststroke pain syndrome showed significant improvements but could not alleviate pain to reach the set endpoint of a ≥50% improvement on the Pain Disability Index in 50% of patients [95].

Meta-analyses and reviews suggest that **Cognitive Behavioral Therapies (CBT)**, including a wide variety of cognitive behavioural psychological therapy techniques, reduce pain intensity, disability, and emotional distress among individuals with FM [96, 97]. CBT did not differ in efficacy except for

superiority for coping with pain from recommended drug therapy (pregabalin and/or duloxetine) at the end of treatment and at long-term follow-up [97]. It seems that CBT reduces potentially dysfunctional brain states and improves clinical outcomes such as pain-related disability in part by reducing catastrophizing. Lazaridou et al. [98] found a substantial reduction in connectivity between insula and primary somatosensory cortex in the CBT group. CBT's effectiveness may thus result directly from their ability to reduce catastrophizing and "normalize" connectivity between salience processing areas such as the insula cortex and primary somatosensory regions that are known to both localize pain and ascribe magnitude to this perception.

Solid evidence is available for a beneficial effect of **physical activity** on FM symptoms. Working mechanisms may partially be explained, besides the musculoskeletal and psychological effects, by restoration of previously reported abnormal patterns of resting state connectivity in FM patients. It seems that after a 3 month schedule of regular physical exercise, several intrinsic brain connectivity patterns underwent longitudinal changes, and especially the connectivity between the right insula and primary sensorimotor cortex displayed a great change in patients with FM [99]. These results were interpreted as a restoration of FM-associated hyperconnectivity between the brain regions involved in pain perception (anterior insula) and sensorimotor regions. Another working mechanism of exercise concerns the involvement of the glutamatergic system on exercise-induced analgesia. Sluka et al. [100] showed that regular physical activity prevents the development of chronic muscle pain by reducing phosphorylation of the NMDA receptor in the central nervous system . These data suggest that the activation of NMDA receptor by Glu in both peripheral and central sites can induce hyperalgesia by phosphorylation of ionic channels, and that physical exercise can prevent its effect [101]. A meta-analysis of six studies indeed concluded that aerobic-only exercise had positive effects on global well-being and physical function in FM patients, reducing pain and improving depressive state [102]. Latest evidence comes from an umbrella review including 37 reviews, considering exercise as an effective way to treat the symptoms of FM syndrome, with a low incidence of related adverse events. Both aerobic exercise and strength training appear effective exercise programs for

the treatment of FM. The greatest evidence was observed in terms of the improvement of pain and quality of life [103].

Conclusions

Perception of pain warns the body against tissue-damaging events. However, when it becomes chronic, pain amplification is perceived that cannot be fully related to somatic or neuropathic processes. Based upon accumulating scientific evidence, we postulate that disturbances in insular Glu/GABA balance contribute to pain, but also lead to other FM-associated symptoms, such as hypotension, bladder and bowel dysfunction, anxiety, and fatigue. Dysautonomia or an abnormal function of the autonomic nervous system, may thus explain the multisystem features underlying the sympathetically maintained neuropathic pain syndrome termed FM. Therapies currently under development that target insular neurotransmitter imbalance either by administering novel selective NMDA receptor modulators or by applying specific electromagnetic stimulation methods, appear very promising and have the potential to provide a true cure for the many pain patients that, at this moment, often find themselves without suitable and effective treatment.

Acknowledgements

Jessica Van Oosterwijck is a post-doctoral research fellow funded by the Research Foundation – Flanders (FWO) [12L5619N and 12L5616N].

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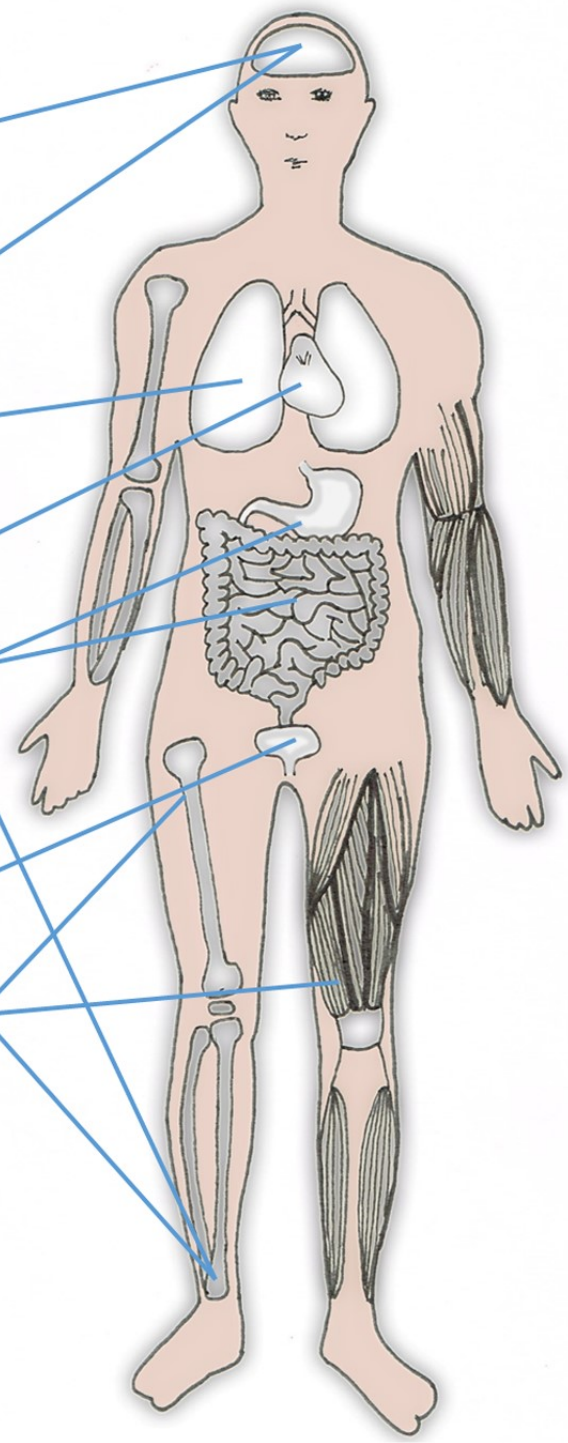
SYMPTOMS

- anxiety, depression, hypersensitivity
- sleeping difficulties, cognitive and memory problems, abnormal fatigue
- dyspnea
- chest pains, palpitations, mitral valve prolapse
- stomach pain, nausea, intestinal cramps
- small fiber pathology (SFP)
- bladder and pelvic pain and discomfort
- widespread muscle and joint pain, muscle stiffness



ASSOCIATED SYNDROMES

- anxiety syndromes
- migraine, obstructive sleep apnea syndrome (OSAS)
- chronic fatigue syndrome (CFS)
- autonomous dysfunction syndromes: postural orthostatic tachycardia syndrome (POTS), orthostatic hypotension,…
- irritable bowel syndrome (IBS)
- interstitial cystitis (IC)
- generalised musculoskeletal pain syndromes