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Neuroimaging of Central Sensitivity Syndromes: Key Insights from the Scientific Literature

Brian Walitt[*,1], **Marta Čeko**[1], **John L. Gracely**[1], and **Richard H. Gracely**[2]

[1]National Center for Complementary and Integrative Health, National Institutes of Health, USA

[2]Center for Pain Research and Innovation, University of North Carolina at Chapel Hill, USA

Abstract

Central sensitivity syndromes are characterized by distressing symptoms, such as pain and fatigue, in the absence of clinically obvious pathology. The scientific underpinnings of these disorders are not currently known. Modern neuroimaging techniques promise new insights into mechanisms mediating these postulated syndromes. We review the results of neuroimaging applied to five central sensitivity syndromes: fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, temporomandibular joint disorder, and vulvodynia syndrome. Neuroimaging studies of basal metabolism, anatomic constitution, molecular constituents, evoked neural activity, and treatment effect are compared across all of these syndromes. Evoked sensory paradigms reveal sensory augmentation to both painful and non-painful stimulation. This is a transformative observation for these syndromes, which were historically considered to be completely of hysterical or feigned in origin. However, whether sensory augmentation represents the cause of these syndromes, a predisposing factor, an endophenotype, or an epiphenomenon cannot be discerned from the current literature. Further, the result from cross-sectional neuroimaging studies of basal activity, anatomy, and molecular constituency are extremely heterogeneous within and between the syndromes. A defining neuroimaging “signature” cannot be discerned for any of the particular syndromes or for an over-arching central sensitization mechanism common to all of the syndromes. Several issues confound initial attempts to meaningfully measure treatment effects in these syndromes. At this time, the existence of “central sensitivity syndromes” is based more soundly on clinical and epidemiological evidence. A coherent picture of a “central sensitization” mechanism that bridges across all of these syndromes does not emerge from the existing scientific evidence.

Keywords

Central sensitization; neuroimaging; fibromyalgia; fatigue; irritable bowel; temporomandibular joint disorder; vulvodynia

[*]Address correspondence to this author at the National Center for Complementary and Integrative Health, National Institutes of Health, 10 Center Drive, Bethesda, MD 20814, USA; Tel: (301) 827-0017; Fax: (301) 480-3159; Brian.walitt@nih.gov.

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INTRODUCTION

Chronic aversive and physically distressing sensations, such as pain and fatigue, occurring in the absence of clinically obvious pathology are common health problems in medical practice. Such experiences are never uniform, yet symptoms often present together in stereotypically recognizable ways. These symptom constellations have been long recognized by physicians and used to define and diagnose distinct somatoform disorders.

The symptoms in these disorders are often specific, related to a particular painful sensation or part of the body. The tenderness and aching pain of the jaw and face found in temporomandibular joint disorder (TMD), the cramping and spasmotic abdominal pains of irritable bowel syndrome (IBS), or the painful burning and irritation of the vaginal opening of vulvodynia syndrome (VVS) serve as examples of such specificity. However, vague and generalized symptoms are also common, as evidenced by the widespread aches and tenderness of fibromyalgia (FM) and the profound fatigue of chronic fatigue syndrome (CFS). Despite the descriptive differences between these disorders, there is a great deal of epidemiologic similarity between them, including female predominance, increases in concomitant medical and psychiatric comorbidity, and impact on health-related quality of life. These disorders also commonly occur together. For all of their differences in clinical presentation, these disorders are quite similar in many clinically important ways.

The scientific underpinnings of these disorders, as well as the mechanisms responsible for their similarities and differences, are not currently known. One prominent idea is that of “central sensitization”, which posits that alterations in central nervous system structure and function lead to an amplification of sensory signaling from which somatoform disorders develop. Such neurologic changes are not currently measurable at the clinical level, perhaps contributing to the clinical “invisibility” of these disorders. However, the proliferation of modern neuroimaging techniques makes it possible to investigate various aspects of the central nervous system and their relationship to these postulated “central sensitivity syndromes”. Here, we review the full array of neuroimaging testing and how these tests have been applied to five different clinical disorders: fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, temporomandibular joint disorder, and vulvodynia syndrome. We describe the neuroimaging findings for each disorder, compare and contrast findings using similar methods between the disorders, and ultimately discuss what is known (and not known) about these disorders and the concept of “central sensitization” based on neuroimaging research. Consistent with the clinical theme of this special issue, we conclude each section with a comment about the clinical utility of the findings. There is a marked divide between neuroimaging methods that provide information about neural mechanisms by averaging the results of a group of subjects and clinical imaging methods that contribute to decisions about a single person. The neuroimaging methods we have reviewed inform much about mechanisms and potentially can aid clinical diagnosis and treatment.

BRIEF DESCRIPTION OF EACH "CENTRAL SENSITIVITY SYNDROME"

Fibromyalgia (FM)

FM is the chronic experience of body-wide pain, fatigue, cognitive dysfunction, and disordered sleep that occurs in the absence of any clinically observable cause [1]. While no longer required for diagnosis, tenderness has been regarded as a key feature of the illness since its inception [2]. FM patients also commonly experience anxiety, depression, and other pain syndromes including IBS, TMD, and VVS. Psychophysical testing has repeatedly demonstrated enhanced sensitivity to a wide array of painful and non-painful stimulation [3–5].

Chronic Fatigue Syndrome (CFS)

CFS is a condition characterized by persistent nonexertional fatigue and post-exertional malaise. CFS shares many of the same symptoms as FMS, including pain, cognitive dysfunction, sleep, depression, and anxiety [6]. The initial descriptions of CFS emerged from an epidemic in Nevada, leading some to attribute its cause to infective agents despite the absence of substantiating evidence. However, the clinical application of the CFS diagnosis does not require any preceding medical illness or trauma. Psychophysical testing in CFS reveals increased sensitivity to pressure applied to multiple body sites and to electrical stimulation of muscle [7, 8].

Irritable Bowel Syndrome (IBS)

IBS is a condition characterized by recurrent abdominal pain, discomfort, bloating, and alteration of bowel habits [9]. Substantial comorbidity with FM, CFS, headaches, and depression is seen in IBS [10]. Psychophysical testing in IBS shows enhanced pain sensitivity to rectal distension by balloon inflation [11] and increased sensitivity in the lower extremity [12, 13].

Temporomandibular Joint Disorder (TMD)

TMD is a condition characterized by recurrent jaw pain, restricted mandibular movement, and experiencing noises during jaw movement [14]. Substantial comorbidity with FM, IBS, headache, low back pain, and depression has been reported. Psychophysical testing in TMD reveals increased pressure pain sensitivity at orofacial and shoulder-neck sites [15, 16].

Vulvodynia Syndrome (VVS)

VVS (or vulvar vestibulitis) is a chronic pain condition in which women experience spontaneous, unprovoked pain in the vulvar vestibule, pain provoked by mechanical stimulation ranging from sexual intercourse to tampon insertion, or both. Substantial comorbidity with other "central sensitivity syndromes" has been reported. Psychophysical studies have demonstrated enhanced pressure pain sensitivity in the vulvar region [17, 18] and at least one study found enhanced pressure pain sensitivity at the thumb [17].

PRIMER ON NEUROIMAGING DESIGNS AND MEASURES

To date, “central sensitivity syndromes” have been studied using several neuroimaging techniques:

Basal Neuronal Metabolic Activity Measurements

Basal neuronal activity refers to metabolic activity of brain tissue that occur when a person is awake and not focused on any particular task or experimental activity. Basal neuronal activity seems to represent the state of idling mind, either as self-directed or wandering thoughts. Basal neuronal activity can be measured with single photon emission computed tomography (SPECT), proton magnetic resonance spectroscopy (H-MRS), functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and arterial spin labeling (ASL) MRI. These different techniques provide information about the amount of neuronal metabolic activity occurring in specific anatomic regions of the brain, some by directly measuring neuronal metabolism and others by inferring metabolism from measures of discrete regional cerebral blood flow (rCBF). These imaging techniques vary significantly in anatomic precision.

Anatomic Measurements

Measurements of anatomic structure of the brain are another neuroimaging technique used to study “central sensitivity syndromes”. Anatomic measurements do not require the participation of any particular task or experimental activity. These studies measure the amount of gray matter (GM) or white matter (WM) of each anatomic region of the brain using a technique called voxel-based morphometry. A second method is diffusion tensor imaging, which takes advantage of the diffusion properties of water in neuronal tissue to provide estimates of the integrity of WM fibers and can provide images of how WM fibers connect to different anatomic areas (tractography). MRI is uniformly used in these studies as it provides the highest amount of anatomic resolution.

Molecular Measurements

Non-invasive measurements of the molecular constituents of *in vivo* tissue can also be performed. Two main techniques are currently in use. H-MRS can measure differences in proton resonance of a particular brain region, yielding a discernable spectra allowing for determination of the region's molecular constituents. Typically, metabolites such as Glutamate, Glutamate/Glutamine, N-Acetylaspartate, Choline, and Creatine are measured and described as metabolite/Creatine ratios [19]. A second method uses Positron Emission Tomography (PET) with radiolabelled molecular ligands to measure the biological availability and tissue uptake. Ligands have been developed to specifically bind molecules such as opioid and dopamine receptors, providing a surrogate measurement of receptor availability.

Evoked Paradigms

Evoked stimuli and evoked task neuroimaging paradigms are the most common neuroimaging designs used in neuroimaging research. Simply stated, evoked paradigms take measurements of brain activity patterns during the administration of stimuli or performance

of a particular task. Neural activity causes discreet, localized alterations in regional cerebral blood flow (rCBF). This observation is used to infer neural activity from changes in rCBF. Thus, these paradigms take advantage of a quintessential scientific observation [20], that the relationship between mental activity and moment-to-moment cerebral blood flow are both predictable and replicable. It is now well established that particular mental activities are associated with surrogate patterns of alterations in the spatial distribution of cerebral blood flow rates [21].

The most common method to measure surrogates of experimentally-evoked neural activity is fMRI Blood Oxygen-Dependent Level (BOLD) imaging. Unlike methods such as positron emission tomography (PET) that use an injectable tracer, the BOLD technique takes advantage of the magnetic character of deoxygenated hemoglobin, which suppresses the fMRI signal from surrounding tissue. The increase in rCBF in response to increased neural activity provides more oxygenated blood than is required to meet the metabolic needs of the active neurons. This oxygenated hemoglobin has less magnetic character, resulting in less suppression in tissue and a corresponding increase in the fMRI signal. These fluctuations in regional blood oxygenation and the resulting signal can be spatially measured in three dimensions to millimeter accuracy using fMRI. Since its inception, BOLD fMRI has been applied to a vast number of scientific questions and has transformed the state of neurological sciences.

One field that has been transformed by the advent of BOLD imaging is the study of pain. Evoked pain paradigms have been able to determine that painful experiences have a recognizable BOLD signature that we describe here as “pain-related networks”. Different types of painful stimulation lead to a similar patterns of increased BOLD activity. The pain-related networks (see Fig. 1) consist primarily of the thalamus, primary somatosensory cortex (S1), posterior parietal cortex (PPC), anterior cingulate cortex, insula (INS), prefrontal cortex (PFC), amygdala (AMY), primary motor cortex (M1) and periaqueductal gray (PAG) [22]. Using advanced statistical learning methods, the predictive power of pain-related network activations has been shown to reliably discern painful heat from non-painful warmth, pain anticipation, pain recall, and social pain [23]. While it has its imperfections and uncertainties, increases in BOLD activity in pain-related networks provide a marker of the pain experience, albeit one that may not be specific for pain [24, 25].

Evoked paradigms using BOLD imaging have not been limited to pain in the study of “central sensitivity syndromes”. BOLD fMRI has also been used to study pain expectations, empathic pain, non-pain sensations, and cognitive tasks.

Treatment Effects

Recently, neuroimaging has been used to collect objective measurements that correlate with symptom change related to treatment. These complex studies use a prospective design, taking measurements prior to and at the completion of a therapeutic intervention. These studies often employ control groups, placebos, patient-reported outcome measurements, and cross-over designs. Attempts to measure treatment effects in “central sensitivity syndromes” have been performed using basal metabolic, anatomic, and evoked imaging paradigms.

NEUROIMAGING OF BASAL ACTIVITY

Historically, the simplest means to image the activity of the brain is to take measurements of its basal metabolism, as these studies require no task to perform or intervention to administer. These studies typically employ a cross-sectional design, comparing a patient group of interest to a control group of demographically-matched healthy volunteers, whom we refer to as “controls”. Early investigators hoped that “central sensitivity syndromes” would have unique basal metabolic signatures that could be used to identify the disorders or serve as biomarkers for symptom severity. The most common method of observing the human brain's basal activity is resting state fMRI (rs-fMRI). During an rs-fMRI scan, subjects are asked to either close their eyes or focus on the projected screen and, most importantly, stay awake. Rs-fMRI detects the BOLD signal that occurs when the brain is in a wakeful “resting” state. There are multiple methods for analyzing BOLD signal data acquired using rs-fMRI, such as Functional Connectivity (rs-fc), Independent Component Analysis (ICA), and fractional Amplitude of Low Frequency Fluctuations (fALFF). Functional connectivity and fALFF usually require a pre-selected region of interest (ROI) or “seed” brain region for analysis. These ROI's/seeds are typically selected based on data drawn from pre-clinical animal models, anatomic imaging, and evoked neuroimaging paradigms.

The rs-fc analysis detects distinct regions that exhibit low frequency fluctuations similar to those of the seed ROI. These regions are said to be functionally connected as they show temporally correlated oscillation patterns in neural activity, regardless of their spatial relationship. A power spectral density (PSD) analysis such as fALFF uses a Fourier transform to separate an ROI's fMRI BOLD signal over time into one that represents each component frequency's power within that time frame. Typically fALFF analysis will divide frequencies into frequency bands such as low, medium, and high. ICA is a data-driven method that does not require any *a priori* seed. ICA regression uses an aggregate imaging dataset drawn up from the entire pool of subjects and detects multiple independent components. These components may then be used as ROI's for further resting state analysis to detect further functional connectivity.

Rs-fMRI has provided insight into organization of intrinsic brain networks. One of the most prominent networks is the Default Mode Network (DMN). The DMN is primarily active when the mind and body are idle. It consists of the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), precuneus, and areas of the parietal cortex. The DMN is also known as the Task-Negative Network (TNN) because it decreases in BOLD signal during directed tasks. It is hoped that measurements of the constitution of the DMN and how easily it deactivates during tasks in the different “central sensitivity syndromes” will provide insight into these disorders.

A comprehensive summary of the application of the different types of basal metabolic imaging to “central sensitivity syndromes” is presented in Table 1.

BASAL NEURONAL ACTIVITY IN FIBROMYALGIA

The initial studies of basal neural activity in FM used SPECT. This first study in 1995 found reduced rCBF within the thalamus and caudate nucleus bilaterally when comparing 10 FM patients to 7 controls [26]. These results were associated with the group differences in tender point counts. Subsequent SPECT studies did not report consistent findings despite larger sample sizes. A SPECT study (n=17) showed rCBF decrease in the right thalamus in FM [27]. However, no differences in basal metabolic activity were found in a study (n=12) using 18F-fluorodeoxyglucose (FDG) PET to evaluate neuronal metabolism [28].

More recent studies of basal neuronal activity in FM have been performed with rs-fMRI. The first study, published only as an abstract (n=10), found group differences in seed-based functional connectivity between the PCC and the INS/orbital cortex [29]. A second study (n=18) using ICA analysis found increased functional connectivity in FM patients between the DMN and the INS and left secondary somatosensory cortex (S2), as well as between another prominent resting-state network, the executive attention network, and right intra-parietal sulcus [30]. Pain at the time of scanning, controlled for age, correlated with greater intrinsic connectivity between the DMN and right INS and between the right executive attention network and bilateral INS. Another rs-fMRI study (n=19) used power spectral density analysis (PSD), a measure of the amplitude of low frequency (0.01–0.10 hz) fluctuations (LFF) within the resting-state BOLD signal, to detect increased PSD in FM patients in S1, supplementary motor area (SMA), AMY and DLPFC compared to controls [31].

The basal metabolic data in FM does not provide a clear biological signature, with inconsistently positive and negative results to date.

BASAL NEURONAL ACTIVITY IN CHRONIC FATIGUE SYNDROME

The initial SPECT studies of CFS patients had conflicting results. Two studies (n=16, 60) reported areas of altered perfusion in CFS patients compared to controls, including the frontal, temporal, parietal, and occipital cortices and basal ganglia, but neither study replicated the findings of the other [32, 33]. A third study (n=16) found no significant decreases in rCBF in CFS patients compared to controls [34]. A fourth study (n=11) reported widespread reductions of absolute CBF in CFS patients using ASL, although two patients showed increases in CBF [35].

SPECT imaging of monozygotic twins, in which one twin fulfills the criteria for CFS and the other does not (n=11), found no rCBF abnormalities between the twins diagnosed with CFS and their healthy siblings [36]. Another study (n=25) measured rCBF ratios using Xenon Computed Tomography after separating CFS patients into comorbid depression and non-depression groups [37]. Targeting six arterial cerebral ROI's and the basal ganglia, it found that CFS patients without any depression had more hypoperfusion, especially along the left and right middle cerebral arteries.

The basal metabolic data in CFS does not provide a clear biological signature, with inconsistently positive and negative results to date.

BASAL NEURONAL ACTIVITY IN IRRITABLE BOWEL SYNDROME

To date, only one study has explored basal neuronal activity in IBS. Forty-two male and 76 female healthy controls were compared to 29 male and 31 female IBS subjects using rs-fMRI [38]. FALFF was applied to the pre-selected seed areas including the INS, S1/M1, and AMY. No significant differences in fALFF were noted between IBS patients and controls. However, male controls had an increased distribution of the high-frequency (HF) band over mid-frequency (MF)/low-frequency (LF) oscillations in the left aINS, bilateral mINS, and bilateral pINS compared to male IBS subjects. Female IBS patients had significantly more HF vs LF oscillations in the left AMY, right HC, and aINS compared to female controls. Within female IBS patients, there was also a positive correlation between discomfort level and the power distribution skewed towards HF in the left aINS.

The significance of this data on determining a biological signature of IBS is unclear. This data support the contention that IBS is confounded by gender heterogeneity.

BASAL NEURONAL ACTIVITY IN TEMPOROMANDIBULAR JOINT DISORDER

Three recent studies have used rs-fMRI and ASL to investigate TMD. The first study (n=8) found increased connectivity in TMD patients between the left aINS and left rostral ACC, left pINS and left parahippocampal gyrus (PHG), and between the right aINS and right thalamus [39]. A larger study (n=17) reported increased connectivity between the MPFC to the retrosplenial cortex and PCC [40]. One last study (n= 15) used ASL to demonstrate increased rCBF in the right cerebellum, right PMC and right ACC, left SMA, globus pallidus (GP), dorsolateral PFC (DLPFC), and dorsal and ventral precuneus [41].

The results of basal neuronal activity measurements in TMD are inconsistent.

BASAL NEURONAL ACTIVITY IN VULVODYNIA

Currently no studies have investigated neural basal metabolism in the brain for individuals diagnosed with VVS.

SUMMARY OF BASAL NEURONAL ACTIVITY MEASUREMENTS IN “CENTRAL SENSITIVITY SYNDROMES”

After reviewing the entire literature, no coherent understanding emerges regarding the relationship between basal neuronal activity and any of the “central sensitivity syndromes”. Further, there is no basal neuronal activity pattern that overlaps between all of the clinical syndromes.

NEUROIMAGING OF ANATOMIC MEASUREMENTS

Measurements of the basal brain state include measures of brain structure. While fundamental brain structure is conserved across humans, there are substantial differences in the structure of particular brain regions and how these regions are connected to other regions

in neuronal networks. While a full understanding of how subtle anatomic changes can alter sensation, emotion and behavior has not been achieved, anatomic measurements can potentially illuminate the biological basis of differences in these experiences. Similar to basal neuronal activity studies, investigators use crosssectional designs to compare regional differences in anatomic qualities between patient groups. Data is then analyzed to determine if there is an anatomic signature for each of the different clinical syndromes.

GRAY MATTER AND CORTICAL THICKNESS

The anatomic quantity of particular brain regions has long been of interest to investigators. While there is a wide array of ways to consider anatomic quality, measurements of the amount of gray matter (GM) using voxel-based morphometry (VBM) is the most common. VBM provides automated whole-brain structural analysis of GM, voxel by voxel [42, 43], providing a measure of the amount of gray matter in discrete anatomic regions. A complementary VBM technique is cortical thickness analysis (CTA) that provides estimates of the thickness of the cortical mantle. VBM results are expressed as either GM *density* or GM *volume*, two related but differentially-derived measurements. The results are described in terms of relative increases and decreases in either density or volume. Here, we describe change in GM but do not distinguish between density and volume.

It is not clear what differences in GM represent. Most assume that GM differences are due to changes in neuronal matter, interpreted as altered numbers of neurons. However, GM measurements may also represent changes in glial matter and non-neuronal cell types, water content and vasculature filling, as well as alterations in regional anatomic structure. Critically, the relationships between GM measurements and neuron function, at both the individual and network level, are not known. The physiological importance of measured differences in VBM has not yet been established.

Interpreting VBM in the study of “central sensitivity syndromes” is therefore complicated. These studies are typically cross-sectional, adding a layer of complexity to the interpretation of VBM results. Decreases in GM may relate to innate differences from birth and development, from injury or atrophy, as a result of processes that guide normal neuronal plasticity, or even the aging process, making it difficult to interpret the clinical significance of regional GM differences or of temporal increases and decreases in GM.

A comprehensive summary of the structural gray matter alterations seen in “central sensitivity syndromes” is presented in Table 2.

GRAY MATTER IN FIBROMYALGIA

The first examination of structural brain alterations in 10 FM patients found a reduction of total GM in a group of female patients, and this GM reduction was accelerated with age [44]. Subsequent and larger studies (typically between 15–30 patients), have failed to show an overall reduction of total GM [45, 46]. Instead, these studies show a pattern of local reductions of GM, with decreases in the MCC and ACC [44, 47, 48], INS [49], MPFC [47], as well as in the lateral PFC [47]. Additional regions have been implicated in FM including

the PCC and the adjacent precuneus [44–46, 48], HC and the adjacent PHG [48, 50], as well as the AMY[47].

Increased GM has also been reported, with increases seen in the basal ganglia, lateral PFC, and INS [45], S1 [46], and in the adjacent PPC [47]. These increases have been shown to have both positive [51] and negative [45] correlations with FM pain sensitivity.

The findings of GM alterations in FM are intriguing. There is apparent consistency of GM reduction in areas of the brain considered to be integral to pain-related networks. Other altered areas of the brain, such as the amygdala and hippocampus, appear relevant to stress response, and prefrontal cortical areas could also be related to the cognitive, emotional and mood aspects of fibromyalgia. However, these areas also involve a vast number of other neurological processes. The consistency of these results is insufficient across studies to suggest an anatomic signature for FM. It is unclear if these GM decreases are causal, represent an endophenotype, or are just an epiphenomenon of FM. Despite these caveats, the observation of structural differences in neuronal tissue has the potential to provide deeper insights into FM.

GRAY MATTER IN CHRONIC FATIGUE SYNDROME

The evidence for GM alterations in CFS is inconsistent. One investigative group has reported reductions in the total GM in two studies (n=13, 28) [52]. Two others found regional GM reductions in the DLPFC (n=16) [53] or the PHG and visual cortical areas (n=26) [54] rather than whole brain changes. A last study (n=25) found no global or regional GM differences [55]. No increases in GM have been noted. None of the observed GM changes correlated with the duration of CFS symptoms, while associations with symptom severity were found by two of the investigators. The amount of GM reduction in the DLPFC correlated with the severity of fatigue experienced by patients [53] while global GM reduction was associated with poor physical activity and lower cognitive speed [52].

These results do not provide a coherent picture of GM alterations in CFS.

GRAY MATTER IN IRRITABLE BOWEL SYNDROME

Six studies have investigated GM alterations in IBS patients. Most report GM reductions in the MCC and ACC [56–59] and the INS [57–60], lateral PFC [58, 61], thalamus [59, 61], and basal ganglia [58, 61]. One study also observed reduced GM in the PCG and AMY of IBS patients [58]. The number of patients in these studies has ranged from around 10 patients [56, 59, 60], to massive investigations, often multi-center, including anywhere between 50 and 200 patients [57, 58, 61].

GM increases have also been observed in IBS patients, with increases observed in the hypothalamus [56], CC and OFC [61], INS [62] and S1/M1 [57, 58]. Both positive correlations [57, 62] and no correlation [57, 58, 62] have been shown between GM increases and symptom severity and chronicity.

The results for IBS resemble those from FM.

GRAY MATTER IN TEMPOROMANDIBULAR DISORDER

Three studies of GM (n= 9, 15, 17) have been performed in TMD patients. GM was reduced in S1 [63], the VLPFC (63, 64), as well as the ACC and PCC, and INS [64]. No studies have observed a relationship between GM decreases and pain duration or severity of symptoms.

The GM reductions above are seemingly contradicted by corresponding increases in GM observed in the same patients. Increased GM of the VLPFC has been reported in two out of the three studies [63], and individual studies also reported increased GM of the S1 and frontal pole [63], and of the INS, thalamus, basal ganglia, and pons [65]. No relationship between increased GM and pain duration has been noted but increased GM of the pons was positively correlated with the severity of jaw pain [65].

The results for TMD provide contradicting evidence. Areas with reduced GM resemble those observed in FM and IBS. However, the reliability of those findings are challenged by similar studies showing increases. The meaning of these results in TMD is not clear.

GRAY MATTER IN VULVODYNIA

The single study performed (14 patients) did not observe any alterations in GM [66].

GRAY MATTER IN “CENTRAL SENSITIVITY SYNDROMES”

After reviewing the entire literature, only a vague suggestion emerges regarding the relationship between GM and the different clinical syndromes. Striking similarities are found between FM and IBS, with decreases in GM in the areas that constitute the pain-related networks. While this suggests some fundamental anatomic similarities, the clinical experience of these disorders is often very different. Some might be tempted to interpret this as evidence of a shared central process.

However, the familiar-seeming pattern of decreased GM has not yet been found in studies of three of the clinical syndromes. There is no consistency in which areas are implicated between the various studies. An anatomic signature of GM does not emerge from these studies. A clear relationship with symptom duration or severity has also not been shown. The true scientific and clinical relevance of these findings is not known.

WHITE MATTER AND FRACTIONAL ANISOTROPY

Another essential anatomic property of neurons is that they are connected to other neurons. These connections are often extensive, creating neuronal “tracts” that serve to connect non-contiguous brain regions to each other. These interconnections typically occur through myelinated neurons, and are typically referred to as the white matter (WM) of the brain. Diffusion-tensor imaging (DTI) is a MRI technique that is sensitive to diffusion properties of water in tissue. This technique takes advantage of anisotropy, the constrained directions in which water contained within long, thin axons can flow. Commonly, this amount of constraint on free water movement is described as fractional anisotropy (FA) and is typically used as measure of WM integrity. Higher FA represents more constraint. Water molecules move more readily along the axon (axial diffusivity, AD) than perpendicular to it (radial

diffusivity, RD). The MRI signal of water obtained with DTI can also be used to estimate the location and trajectories of WM [67] thereby providing pictures of WM tracts in a process referred to as “tractography” [68]. Measures frequently reported in addition to FA include axial, radial, and mean diffusivity.

Tractography performed with DTI provides maps of WM connectivity. Deeper understanding regarding how neuronal network structure is linked to sensation, emotion, and behavior may be possible using this technique. Anisotropy measures can provide a sense of axon quantity and information in regard to three-dimensional paths of axons. However, it is not clear what group differences or changes in anisotropy actually represent. There is some evidence that lower FA and AD, with typically corresponding RD and MD increases, are associated with increased size and branching or crossing of WM tracts, microstructural cellular changes and edema, disruptions to axonal membrane, and decreased myelination [69]. Alterations in FA (both decreases and increases) can also represent differences related to non-pathologic alterations in neuronal plasticity. It is also unclear how to interpret the regional variability of anisotropic change. Similar amounts of anisotropy may have differential impact on various neuronal functions depending on brain region.

Interpreting anisotropy in the study of “central sensitivity syndromes” is therefore challenging. Current study designs make it impossible to discern if differences in anisotropy are related to innate birth and developmental differences, from injury or atrophy, as the result of processes that normally guide neuronal plasticity, or the aging process. The clinical implications of changes in anisotropy are not known.

A comprehensive summary of the structural white matter alterations seen in “central sensitivity syndromes” is presented in Table 3.

WHITE MATTER ALTERATIONS IN FIBROMYALGIA

Five studies of WM have been performed in FM. One study (n=26) found total cortical WM to be reduced, with altered FA in WM regions connecting brain areas with GM alterations [47]. A second study (n=30) found FA increased in the lateral PFC, ACC, AMY, HC, and S1, and reduced in the thalamus, thalamocortical tract, and INS [50]. Increasing pain, fatigue, and anxiety scores correlated with increased FA in the lateral PFC. Reduced FA in the thalamus was also reported in a third study (n=19) that correlated with pain reporting [70]. Recently, contrarian findings of reduced FA that correlated with increases in pain reporting were found in 19 patients in the portion of the corpus callosum that connects to S1 [71]. Age also appears to be an important factor in anisotropy in FM. Older FM patients (n=14) demonstrated lower FA in a region of the PCC adjacent to a region of reduced GM while younger FM patients (n=14) had higher FA in the anterior thalamic radiation/anterior limb of internal capsule adjacent to the putamen [45].

These results do not provide a consistent picture of WM change in FM.

WHITE MATTER ALTERATIONS IN CHRONIC FATIGUE SYNDROME

One study has not demonstrated any alterations of global FM in CFS (n=19) [53], while another study reported decreased WM in the occipital lobe of 26 patients [54].

WHITE MATTER ALTERATIONS IN IRRITABLE BOWEL SYNDROME

Two studies of WM have been performed in IBS. One study (n=10) found increased FA adjacent to the INS (fornix and the external/extreme capsule) [72]. Correlations between FA and IBS symptom reporting were noted, but only in brain areas where patients did not have altered FA compared to healthy controls. Another study (n=33) found decreased FA in or adjacent to the thalamus, basal ganglia, and sensory-motor areas, and the PCC, as well as increased FA in or adjacent to MPFC and corpus callosum [73]. In this study, patients also had reduced WM in the GP and increased WM in the thalamus, internal capsule, and corona radiata projecting to sensory-motor regions, and tractography measures suggested a greater magnitude of connectivity between the thalamus and PFC, and between medial dorsal thalamus and the ACC, as well as lower degree of connectivity between the thalamus and GP.

These results do not provide a consistent picture of WM change in IBS.

WHITE MATTER ALTERATIONS IN TEMPOROMANDIBULAR JOINT DISORDER

Two investigative groups have measured WM change in TMD. One group (n=17) reported widespread reductions of FA, primarily in the corpus callosum, internal and external capsule, in tracts associated with the thalamus and S1, and between the genu of the corpus callosum and the DLPFC, as well as increased connectivity between the corpus callosum and the frontal pole [74]. In this cohort, FA in WM tracts connecting the SMA, CC and in the corticospinal tracts were related to helplessness. A different preliminary study (n=9) observed reduced WM volume in the MPFC and ACC [64].

These results do not provide a consistent picture of WM change in TMD.

WHITE MATTER ALTERATIONS IN VULVODYNIA SYNDROME

No studies have investigated anisotropy in VVS.

WHITE MATTER IN “CENTRAL SENSITIVITY SYNDROMES”

After reviewing the entire literature, no consistent picture emerges regarding the relationship between white matter and the different clinical syndromes. The data that currently exists are sparse and inconsistent, both within and between the clinical disorders.

NEUROIMAGING OF MOLECULAR BIOLOGY

Molecular Measurements

In vivo measurements of receptor mechanisms and metabolite concentrations represent an exciting area of neuroimaging. Neurotransmitters have an essential role in neuronal performance and it is self-evident that pharmacological alterations of neurotransmission can profoundly alter subjective experience, as evidenced by opioids, ethanol, psychedelics, and antidepressants. Molecular imaging techniques, such as H-MRS and PET imaging, have only been recently applied to the study of “central sensitivity syndromes”.

H-MRS imaging is challenging to interpret. The technique requires pre-selecting a small number of single voxels in a region of interest (ROI). The spectral signal is prone to artifact and a careful “shimming” process is required to obtain quality data. Glutamate is a major excitatory neurotransmitter. Gamma-aminobutyric Acid (GABA) is a major inhibitory neurotransmitter. These metabolites are implicit in all neurological processes and their anatomically-specific effects on sensation is not known. N-Acetylaspartate (NAA) is the second most common molecule within the brain, found predominantly in neuronal cell bodies, which is why it has been suggested as a neuronal marker. Choline (Ch) is believed to reflect cellular membrane content, such as myelination. Typically, Glu, Glutamate/Glutamine (Glx), NAA, and Ch are described as metabolite/Creatine (Cr) ratios, making all H-MRS data relative values rather than absolute values. Ratios are used because of absolute values vary considerably between scanning sessions within the same individuals. Complicating interpretation of these studies is that the role of these metabolites in brain function is not fully established, small numbers of patients, non-reporting of negative results, and the performance of multiple statistical comparisons without appropriate adjustments. These issues are typically addressed by mentioning the `pilot' nature of the study. For these reasons, additional caution is advised when attempting to interpret such results.

A comprehensive summary of molecular alterations seen in “central sensitivity syndromes” is presented in Table 4.

Molecular Measurements in Fibromyalgia

Several studies have found alterations of metabolites in discrete anatomic areas in FM when compared to controls. A study of the DLPFC (n=21) reported significantly elevated variability of Cho within the DLPFC. This finding was reported to correlate with clinical pain, but this result appears related to the inclusion of outliers with low pain scores (VAS<4) that are typically excluded from FM studies [75]. Increased levels of Glx in the aINS of FM patients (n=19) have been observed compared to controls [76]. Increased levels of Glx in FM patients (n=10) were also found in the PCC, which were correlated with pain catastrophizing [77]. Increased levels of Glx in the bilateral VLPFC in FM (n=12) have been observed [78]. FM patients (n=10) have also been shown to have increased levels of Glx in the posterior gyrus which was correlated with depression [79]. Increased levels of Glx compounds in the rAMY in FM (n=28) have also been found [80]. Two additional studies is FM (n=15, 16) found reduced NAA in hippocampus [48, 81, 82]. One study discovered

decreased GABA in the right aINS in FM patients (n=16) and a positive correlation with GABA and slightly intense pressure thresholds in the pINS [83].

Two studies have used PET to study molecular aspects of FM. A small study (n=6) reported decreased dopamine uptake within the medial thalamus, substantia nigra, ACC, HC, and INS [84]. A study of μ-opioid binding in FM (n=17) found reduced potential in the bilateral nucleus accumbens, left AMY, and right ACC [85].

These results do not provide a consistent picture of molecular alterations in FM. It appears that heterogeneous differences can be demonstrated in any region that is targeted.

Molecular Measurements in Chronic Fatigue Syndrome

Two small studies (n=8, 8) using H-MRS have found increased Cho/Cr in the basal ganglia and occipital cortex in CFS patients [86, 87].

Molecular measurements in Irritable Bowel Syndrome

One study (n=15) has used H-MRS to investigate altered metabolite concentrations in IBS [88]. They found a reduction of Glx within the HC in IBS patients that was negatively correlated with emotional stress indicators.

Molecular Measurements in Temporomandibular Joint Disorder

The only study using H-MRS in TMD (n-=11) found increased Gln within the right INS, and increased NAA, and Cho in the left INS [89].

Molecular Measurements in Vulvodynia

No studies using PET imaging or H-MRS have been used to investigate brain alterations as a result of vulvodynia.

Molecular Measurements in “Central Sensitivity Syndromes”

After reviewing the entire literature, no consistent picture emerges regarding the relationship between molecular measurements and the different clinical syndromes. The data that currently exists is sparse and inconsistent, both within and between the clinical disorders.

NEUROIMAGING OF BRAIN ACTIVITY BY EVOKED STIMULATION AND TASK PERFORMANCE

The majority of neuroimaging studies of “central sensitivity syndromes” have used evoked paradigms using the fMRI BOLD method. To effectively measure the relatively small changes in BOLD signal that could be overwhelmed by short-term drift in the sensitivity of early scanners, the evoked study designs contrasted different alternating shortduration (seconds) blocks of stimulus condition, usually an “on” condition and an “off” condition. During each block, multiple fMRI brain images are obtained. An example of such a design can be seen in Gracely (2002) which employed a 3s TR (repetition time) to obtain 10 brain images during a 30s pressure stimulus “on block” and during a 30s stimulus “off block” [90]. These alternating blocks are then repeated multiple times. The analysis compares the

effects of block type (i.e. “on” compared to “off), where appropriate statistical testing such as a t-test or Z-test make comparisons of BOLD signal at each voxel. If blocks are not dichotomous, such as when multiple different stimulus intensities are administered, the statistic can be a regression between the block stimulus and the evoked BOLD signal.

Alternatives to the traditional fMRI block design continue to be developed. “Event-related” designs assume that each stimulus is an event at a single point in time. This method models the expected hemodynamic response to the event. This response is measured using a smaller time scale than the typical 2–3s time of an fMRI image (TR) by altering the onset time (jittering) of the event in relation to the image time. This allows for the sampling of BOLD signal at discrete time points within the duration of a TR. This method can be used to assess events in a random sequence, including uncontrolled events, such as errors in task performance.

In parallel with study design, fMRI analytic methods have also advanced. Methods such as ICA are able to evaluate complex responses and divide them into a smaller number of response components. Both this method and eventrelated designs have been used in studies of “central sensitivity syndromes”.

EVOKED PARADIGMS USING PAINFUL STIMULATION

The first generation of evoked pain stimulation studies evaluated the brain activity in block designs in which the effect of pain stimulus “on” conditions were compared to pain stimulus “off” conditions. The results of statistical comparisons were 3-dimensional statistical maps of brain regions with significant “activations”. This led to a seminal observation, that painful stimulation predictably caused a pattern of activation representing pain-related networks [91, 92]. In the evaluation of patient populations, higher-level analyses contrasted these results between groups, usually a patient group and a group of healthy control subjects.

PAINFUL PRESSURE STIMULATION IN FIBROMYALGIA

One of the first fMRI studies of FM compared the effects of painful blunt pressure in FM patients to controls. This study contained two design features that have been widely used in subsequent experiments. First, it applied blunt pressure to the thumb nail bed. This method acknowledged that the characteristic tenderness of FM was not confined to defined tender points but was present throughout the body [5]. Application of painful pressure to the thumb also assumed that the tenderness of FM is not solely a property of muscles but rather a property of ubiquitous deep mechanical nociceptors located in many tissues. Second, the design compared the effects of thumbnail pressure in two conditions [90]. In the first, the “equal stimulus pressure” condition, controls received similar stimulus pressures delivered to the FM patients. Controls reported the stimulus to be either minimally painful or not painful and had no significant alterations in BOLD activity patterns related to the pressure stimulus. In contrast, FM patients reported the same amount of pressure to be moderately painful, which was accompanied by a pattern of increased BOLD contrast. This pattern included the contralateral S1 and INS, inferior parietal lobule (IPL), bilateral S2, and centralized regions in the ACC, which are consistent with activation of pain-related networks. However, in the “equal subjective pain” condition, the stimulation pressures used

in the controls were adjusted (approximately doubled) to evoke moderate pressure pain that was equal to that reported by FM patients at lower pressures. In this equal pain condition, statistically similar BOLD activations of pain-related networks were observed in both groups.

This experiment made one of the key observations in FM. Patients with FM had both increased pain reporting and pain-related network activations at pressures that did not evoke subjective pain or pain-related network activation in controls. However, both subjective pain and pain-related network activation became equal in controls when they were given a stronger stimulus. This observation demonstrates that, at least in part, painful stimulation is augmented in FM. It is the first objective evidence that the differential experience of pressure pain in FM has a reproducible biological correlate, making the complaint of tenderness “real” rather than exaggeration or malingering. However, it should not be of much surprise that a biological correlate of tenderness would be increased in a population selected based on having high levels of tenderness. Demonstrations of increased pain-related network activation successfully demonstrate that there are group differences in tenderness but does not explain why those differences exist.

This study design using objectively and subjectively matched painful pressure has been replicated in studies using similar methods [93] and *a priori* defined ROI in the INS [94]. Additional replications have used advanced methodology, such as ICA, to independently assess the multiple components present in the results and consider other relevant factors, such as the duration of the effect [95]. This analysis found similar results of enhanced cerebral responses to equal painful pressures (4 kg) and equalization of enhancement when controls were stimulated with increased pressure (6.8 kg) to match the subjective intensity reported at lower pressures in the FM group. This data-driven study also found that the brain activity evoked by a 9s stimulus persisted for 18s in both FM patients and controls. Temporal factors were manipulated in another study using an event-related design that models the hemodynamic function of a short stimulus in contrast to a block design. Instead of longer stimuli (9–30s) used in the block design experiments, brief (2.5s) pressure stimuli to the thumb were delivered at unpredictable times [96]. Sixteen FM and 16 controls received stimulus intensities matched for equal subjective pain magnitude (50 mm on a 100 mm pain intensity VAS). Both groups showed similar results for evoked activity in brain regions related to sensory input and attention. There were no regions that showed greater activity in FM relative to controls, while significantly greater activity in controls compared to FM was observed in contralateral thalamus and in bilateral rostral ACC, a region associated with pain inhibition. This result was interpreted as evidence of deficient descending inhibition in FM.

PAINFUL HEAT STIMULATION IN FIBROMYALGIA

Augmented pain sensitivity in FM is not confined to pressure [5, 97]. One of the earliest fMRI studies used objective and subjective matching of FM patients (n=9) and controls (n=9) found no difference using subjectively matched painful heat [98]. Application of the same objective 47°C stimulus to both groups produced a number of activations in both groups, with the FM group showing significantly greater activation in contralateral INS. The

lack of significance in other regions found with pressure could be due to differences between pressure and heat sensitivity in FM and to the small number of subjects in the heat study. A later study (n=13) compared heat pulses repeated at fast (0.33 Hz) and slow (0.17 Hz) frequencies [99]. Stimulus temperatures were matched subjectively to produce moderate pain sensations. No difference was found between FM and controls. In each group the fast frequency produced enhanced subjective pain and brain responses, an effect termed "windup" [100]. Combining the groups using an ROI analysis revealed this temporally-enhanced pain was associated with increased brain activity in ipsilateral and contralateral thalamus, medial thalamus, S1, bilateral S2, mid -and posterior INS, rostral and mid-ACC.

PAINFUL CHEMICAL STIMULATION IN FIBROMYALGIA

Increased sensitivity to painful stimulation in FM has been found for other painful modalities, including electrical stimulation and intramuscular injection of hypertonic saline [5]. Intramuscular injections are qualitatively different from brief fMRI stimuli, producing a more prolonged, widespread and natural sensation. BOLD fMRI has been used to assess the effect of intramuscular injection. Rather than use the common methods of injecting hypertonic saline or capsaicin, the investigators injected protons (low pH) and prostoglandin E [2] to minimize tachyphylaxis [101]. Repeated injections in the left extensor carpi radialis brevis muscle in FM patients (n=8) extensively activated pain-responsive networks while these injections in controls (n=10) resulted in a reduced pattern of activation limited to cingulate cortices and S1. A between group comparison revealed a greater activation in the left aINS in FM, further evidence of the involvement of INS in pain in general and FM in particular.

NATURAL INCISION PAIN IN FIBROMYALGIA

Other natural pain studies used an experimental incision of the volar forearm. The initial study (n=18) collected BOLD fMRI scans before and after such an incision. FM patients showed significantly greater activations in ACC, MCC, DLPFC, SMA and midline thalamus while controls showed greater activations in right lateral thalamus [102]. The authors then performed two logical follow up studies. The first essentially repeated the original study with the inclusion of an important control group, patients with rheumatoid arthritis, to determine if the initial results could be generalized to any chronic pain condition [103]. The results for FM (n=17), but not rheumatoid arthritis (n=16), were similar to the results for FM in the first study, providing additional evidence for a frontal cortex and cingulate mechanism mediating FM pain. The second follow up study focused on testing for primary hyperalgesia at the incision site (punctate pressure) and secondary hyperalgesia (pin prick) in uninjured skin adjacent to the incision site [104]. After the incision, activity evoked by stimulation in the primary zone at the incision site was similar in all groups. In contrast, activity evoked by pinprick stimulation in the secondary region adjacent to the incision was greater in left DLPFC in FM patients while activity evoked in bilateral SMA was greater in controls.

These studies are notable for the use of a natural stimulus, the use of controls that distinguish between FM pain and that of a second painful disorder, and investigations of alterations in pain processing at a site of injury. Future studies could expand these controls

to include other painful conditions and “central sensitivity syndromes” and expand the testing to include stimulation known to be altered at primary (blunt pressure, heat) and secondary (A-beta mediated mechanical allodynia tested by mechanical or electrical stimulation) regions.

ANTICIPATION OF PAIN IN FIBROMYALGIA

Functional MRI block designs typically alternate stimulation with stimulation-free periods in a predictable fashion. Subjects know during “off” periods in block design studies that they are about to receive an unpleasant or painful stimulation as well as a general idea about when this stimulation will occur. It would be surprising if this anticipation was not measurable by fMRI. Anticipation of painful pressure applied to the thumb (n=12) found significantly greater activation in FM in the DLPFC, PAG and PPC [105]. Activity in the PAG is often associated with descending pain modulation, in particular analgesic networks. The authors interpreted this PAG activity as a conditioned preparatory response in which analgesic systems are activated in advance of the stimulus, suggesting that alterations responsible for greater clinical pain and experimental pain sensitivity also result in a more robust activation of regions involved in pain inhibition during painful expectation. However, FM patients still experienced the evoked stimuli as more painful than controls despite this conditioned response.

OBSERVING OTHER'S PAIN IN FIBROMYALGIA

Brain activity evoked by observing pictures of injury or neutral images (n=23) revealed an attenuated response in FM in the pain-related network, including thalamus, ACC, DLPFC, S1 and M1[106]. This reduced response was interpreted as reduced empathy to avoid arousal and aversive emotions. Alternatively, this effect could reflect increased baseline activity in these regions that may limit further increases in activity, an adaption effect in which the pain of others is referenced to self-pain, or be related to other non-pain cognitive processes.

PAINFUL PRESSURE OF THE THUMB IN VULVODYNIA

One study compared 24 FM, 24 VVS, and 13 controls using a thumb pressure pain block design paradigm [107]. The “equal subjective pain” experiment evoked similar activations in all groups while overlapping activations in the INS were greater in both FM and VVS compared to controls. In comparison to controls, VVS patients also displayed greater activations in dorsal ACC, PCC and thalamus. This result suggests that the psychophysical and neuroimaging evidence of generalized augmented pain sensitivity for FM extends also to VVS.

PAINFUL PRESSURE OF THE VULVA IN VULVODYNIA

Similar pressure stimuli were delivered to the posterior vulvar vestibule with provoked-only VVS (n=14) and controls [108]. These stimuli were painful only to the VVS group and concomitant activations were found in the INS, S1, PMC, and dorsal ACC. A second study (n=24) used subjectively-matched pressure and found no differences in activations to stimuli

delivered to the introitus at the 5 o'clock position, lateral to the hymenal ring. Only a single difference in deactivation was found; VVS patients had less deactivation in IPL than controls [107]. When VVS patients were divided into two subgroups based on the presence of unprovoked, ongoing pain in one group (n=10) and provoked-only pain in the other group (n=14), the provoked-only group demonstrated greater activation in the precuneus. The absence of an effect on pain-related networks in this study, despite a greater number of subjects, may be related to using only subjectively matched stimuli and the inclusion of patients with non-provoked pain. These design choices may have attenuated the pain provocation effects in this subgroup and increased the heterogeneity of the patient sample.

PAINFUL PIN PRICK STIMULATION IN TEMPOROMANDIBULAR DISORDER

One study (n=19) has investigated painful pin prick stimulation in TMD. Pricking pain was produced using a 1mm filament delivered with an amplitude high enough to produce pain and adjusted to evoke a rating of 5 on a 0–10 scale when applied to the left mental nerve region. Brain activity evoked by this stimulus was evaluated under hypnotic conditions of hypoalgesia, hyperalgesia, and in a nonhypnotic control condition [109]. BOLD activation was evoked in six regions that included contralateral S1 and pINS. Clinically substantial alterations in the pain and unpleasantness ratings occurred in the expected directions during hypnotic manipulation. Suggestions of hypoalgesia resulted in brain activity only in contralateral INS, while the opposite suggestion of pain hyperalgesia resulted in increased activity in contralateral INS and in contralateral PMC and ipsilateral parietal cortex. In addition to the congruent reduction of activity and ratings during hypoalgesia, there was dissociation between increased ratings and unaltered activity in contralateral S1 in the hyperalgesia condition. This suggests that S1 function is specialized for localizing pain rather than grading sensory magnitude and/or that hypnotic modulation of pain occurs at later stages in sensory processing.

PAIN EVOKED BY TEETH CLENCHING IN TEMPOROMANDIBULAR DISORDER

Teeth clenching can be painful in TMD, providing a unique natural stimulus. Only a few studies have used this technique. Two low-powered studies found evidence for TMD-specific activation in ACC [110, 111]. A third assessed the influence of clenching on measures of handgrip force in healthy controls [112].

PAINFUL RECTAL DISTENSION BY BALLOON EXPANSION IN IRRITABLE BOWEL SYNDROME

A number of studies have evaluated brain activity associated with sensations evoked by rectal distension, including both PET and fMRI neuroimaging methods. A meta-analysis of eighteen studies (5 PET), performed between 2000 to 2010, focused on the effects of distension in IBS without the influence of other factors [11]. These studies included healthy controls and/or IBS patients and delivered either fixed balloon pressures ranging from 15 to 60 mm Hg or, similar to the method applied to FM [90], used subjectively calibrated stimulation. The results of stimulation in healthy controls were classified as activating brain

regions associated with sensory processing, emotional arousal, and attention or modulation of arousal [13, 113–118]. Stimulation in IBS patients activated similar sensory and emotional arousal regions, and activated additional regions not observed in healthy controls [13, 114–122]. Activated regions involved in attention and arousal were different in the two groups.

SUBLIMINAL BALLOON DISTENSION RESPONSES IN IRRITABLE BOWEL SYNDROME

One study administered rectal balloon distensions that were below threshold, i.e. not detected or perceived by the subject [123]. The purpose was to minimize the effects of stimulus-related cognitive processes. Using a novel analysis measuring the overall extent, or volume, of cortical activity, 10 IBS patients showed a greater overall volume of activations in comparisons to 10 control subjects. This effect was interpreted as evidence of increased sensitivity without the influence of cognitive processes. In a commentary article, Naliboff and Mayer [124] point out that the observed effects could be related to known effects evoked by stimulus anticipation as discussed above, and that it may not be possible to completely eliminate cognitive influences in these types of experiments. Their commentary also notes that the novel measures of overall brain activation do not permit interpretations based on the pattern of effects and thus cannot provide evidence for several possible IBS hypotheses.

ANTICIPATION OF PAIN IN IRRITABLE BOWEL SYNDROME

As noted above for FM, anticipation of painful pressure evoked activity in DLPFC, PAG and PPC. In IBS (n=14), anticipation of rectal balloon inflation revealed significantly less reduced activity in right pINS and bilateral dorsal brainstem compared to controls [113. 117]. The results of both anticipation and distension were interpreted as a possible deficit in pain inhibition in IBS. Evidence for deficient inhibition has also been found for FM, although the increased activation in PAG during anticipation described above is inconsistent with deficient inhibition.

These different interpretations identify critical issues for future studies. Thumb and rectal stimuli likely vary significantly on dimensions of control, fear of bodily harm and other factors that influence physiological effects, such as the engagement of pain inhibitory systems. These psychological effects are assumed to be greater with a rectal balloon versus voluntary insertion of a thumb in a device that allows immediate removal [97].

EVOKED FATIGUE IN CHRONIC FATIGUE SYNDROME

The development of evoked fatigue paradigms that can be performed in the neuroimaging environment is very challenging. An initial attempt (n=12) employed guided visual imagery to elicit fatigue [125]. The authors report that CFS patients found the images more fatiguing than controls, although the measure did not estimate the magnitude of the effect. The task correlated with increased BOLD activity in the OPC, PCC, dorsal MPFC, PHC and

decreased activity in DLPFC and dorsal MPFC. A reverse-pattern of activations was noted during guided visual imagery to elicit anxiety.

It is very difficult to interpret these findings. “Fatigue-responsive networks” have yet to be discovered, if they exist at all. Much more study appears to be required.

MEASURING THE INFLUENCE OF NON-PAIN FACTORS ON EVOKED PAIN USING MULTI-FACTOR STUDY DESIGNS

The seminal studies demonstrating pain and non-painful sensory augmentation in “central sensitivity syndrome” patients have been followed by multi-factorial designs that assess the influence of other variables on painful stimulation.

In a classic example of such a study (n=16), FM patients and controls received painful laser stimuli while viewing pictures with positive, neutral or negative emotional content from the International Affective Picture System [126]. The painful stimuli and pictures were presented both alone and together. In controls, pain ratings were lowest during presentation of the positive pictures and highest during presentation of the negative pictures. In FM patients, ratings were not reduced during positive pictures, and the brain activations during these positive pictures (ACC, S1, S2, INS) were attenuated in patients compared to controls. The combined psychophysical and functional imaging results suggest a failure to properly activate pain inhibitory systems. In a similar design using IBS patients (n=15) and controls [127], brain activity evoked by rectal balloon distension was evaluated under a condition of psychological distress (public speaking and a mock emergency requiring the scanner) and on a different day, a condition of relaxation (using practiced progressive muscle relaxation). Altered brain activity in IBS patients, with enhanced activity in INS and VLPFC and diminished activity in subgenual ACC and DLPFC, was observed when compared to controls during the stress condition, even after statistical adjustments for anxiety. Comparably reduced activity was noted in IBS patients only in the INS during the relaxation condition, which was fully attenuated when anxiety was considered.

Thus, these seemingly similar manipulations of psychological state in two “central sensitivity syndromes” produced different results. The effect of pictures in FM was confined to altered effect of the positive, pain-inhibiting mechanism, while the effect of stress/relaxation in IBS was related to multiple changes in the negative, pain enhancing condition. Firm conclusions must wait for more robust studies employing similar manipulations across multiple conditions.

Multi-factor study designs can also assess the association of any particular psychological construct, such as catastrophizing [128], depression [129] or perceived dyscognition, with evoked pain BOLD activations to identify regions where such constructs may putatively modulate pain-evoked activity. Multi-factor studies can also use experimental pain sensitivity as a factor. This approach has been used to assess brain effects related to age [45] or the response to sham acupuncture [130]. In IBS, there is evidence that enhanced sensitivity to rectal stimulation habituates to repeated stimulation over time. Using this effect as an independent variable, one study observed alterations in neural networks that

suggest that this habituation is associated with both a top-down and AMY-related reduction in attention interference [131].

EVOKED PAIN IN "CENTRAL SENSITIVITY SYNDROMES"

A substantial body of scientific evidence exists using evoked pain paradigms in "central sensitivity syndromes". After reviewing the entire literature, a consistent picture emerges, that of increases in activation of pain-related networks that correlate with increases in pain reporting. It seems clear that the "tenderness" of FM, the "provoked vulva pain" of VVS, and teeth-clenching pain in TMD have objectively measurable biological correlates, demonstrating that such evoked complaints are "real" experiences rather than being a personal choice, an exaggeration, or malingering.

However, this seminal finding appears to create more questions. The neuroimaging results that are consistent with pain augmentation are still very heterogeneous, with studies interpreting substantially different patterns of BOLD activity as representative of the same process of augmentation of pain-related networks. The reason for these differing results is unknown, likely important, and could potentially undermine prevailing scientific interpretations. Further, the typical symptoms of "central sensitivity syndromes" occur in the absence of any known stimulation. It is unclear how pain augmentation could explain the experience of symptoms in the absence of known provocation. Also, many of the distressing symptoms in "central sensitivity syndromes", such as headache, unrefreshed sleep, and depression, cannot be readily studied using evoked paradigms or explained by sensory augmentation. Lastly, sensory augmentation may represent a causal pathologic change, a perceptual alteration related to other causal mechanisms, or an antecedent perceptual predisposition that predates symptoms. The cross-sectional designs of the aforementioned studies cannot provide the needed temporal insights. Despite the importance of the scientific insight, it seems unlikely that pain augmentation is the key causal factor in "central sensitivity syndromes".

NEUROIMAGING OF BRAIN ACTIVITY EVOKED BY NON-PAINFUL STIMULATION

Interestingly, a growing body of evidence suggests that the sensory hypersensitivity is not confined to painful stimulation in "central sensitivity syndromes" but found also for non-painful stimulation.

Non-Painful Stimulation in Fibromyalgia

Functional MRI measures of brain activity evoked by non-painful auditory, visual and tactile stimuli were compared between FM patients (n=35) and controls. The FM patients showed attenuated responses at early sensory processing stages in primary visual and auditory cortex and augmented responses at subsequent processing in INS [3]. The magnitude of these differences correlated with FM symptoms of perceived hypersensitivity as well as scores on the Fibromyalgia Impact Questionnaire (FIQ). These findings suggest that sensory augmentation is not confined to pain processing in FM.

Non-Painful Stimulation in Irritable Bowel Syndrome

Brain activity evaluated by cortical evoked potentials to auditory tones revealed increased early sensory components in IBS, suggesting a cortical hypersensitivity to sound [132].

Non-Painful Stimulation in Temporomandibular Disorder

Non-painful tactile stimulation has been assessed in TMD by both fMRI and MEG. The fMRI study used 4s-duration vibrotactile flutter stimuli with 400 μm amplitude delivered at 26 Hz, stimulus parameters allowing comparison to optical imaging results in squirrel monkeys [133]. Ratings suggest that a group of 13 TMD patients perceived this flutter stimulus to be more intense than controls. This stimulus activated multiple regions in both groups, including regions involved in somatosensory processing (contralateral S1, bilateral S2, bilateral INS) and association areas (bilateral ACC, ipsilateral IPL and DLPFC). Each group also had particular activations significantly greater than those from the other group. Some subregions within contralateral S1, S2, and INS were shown to have significantly greater activations in TMD while other subregional activations were greater in controls. Additional activations, including bilateral thalamus, auditory cortex, ACC, and contralateral AMY, were greater in the TMD group. The activations in auditory cortices and AMY were surprising findings.

These differences in tactile processing in TMD patients and controls were consistent with a MEG study of air puffs to the face of TMD patients (n=8) and controls. The greater temporal acuity of MEG revealed that the evoked responses in TMD, termed equivalent current dipoles, had earlier onset times, were longer in duration, were less tightly grouped, and had different distribution of response power over the 1s response time [134].

Non-Painful Stimulation in “Central Sensitization Syndromes”

The observation that sensory augmentation is not confined to pain in “central sensitization syndromes” is an important one. It suggests that enhanced processing is not confined to nociception but occurs with all types of sensory information, and that such sensory augmentation does not always lead to symptomatic complaint.

NEUROIMAGING OF BRAIN ACTIVITY EVOKED BY COGNITIVE TASKS

Subjective Dyscognition and Objective Cognitive Testing

Feeling that one's cognitive faculties are disturbed is a common complaint in “central sensitivity syndromes”. These are described as difficulties with remembering details, word–finding difficulties, an inability to properly concentrate, being easily distracted, muddled-thinking, and “feeling fuzzy”. The subjective perception of cognitive difficulties has been referred to informally as “fibro fog” and more recently as “dyscognition” [135]. Extensive surveys of patients place considerable importance on perceived cognitive complaints, ranking dyscognition in the top five symptoms that include also non-restorative sleep, pain, fatigue, stiffness and aching joints [136, 137]. However, dyscognition has only recently been classified as a prominent symptom of FM by physicians and research investigators [1].

Unlike subjective reports of widespread pain, subjective reports of cognitive difficulties can be evaluated to some degree by objective cognitive testing. These tests are believed to measure different aspects of the cognitive process, such as attention, concentration, memory, verbal fluency, and spatial processing, determining performance usually as a function of accuracy and speed. There are a great many different tests that are available and comparing performance scores between testing platforms is often difficult.

Pain, Sleep Problems, Negative Mood and Medication Side Effects are Sufficient to Impair Objective Cognitive Function

It is not surprising that the experience of adverse symptoms would impair cognitive function. The effects of pain on the ability to concentrate and attend to tasks have been well documented [138, 139]. Similarly, disordered sleep has adverse effects on multiple domains of cognitive function [140–142]. Negative mood also impacts function [143–145]. Finally, "It is entirely reasonable to expect that medications, some with warnings to not operate heavy machinery, may cause poor functioning on cognitive tests" [135]. This is an important consideration since patients with these disorders often use multiple medications that impact central nervous system functioning. All studies that evaluate the cognitive deficits of "central sensitivity syndromes" are confounded by these comorbid issues.

Cognitive Testing in Fibromyalgia

The results of objective cognitive testing in FM have been summarized in several reviews [135, 146, 147]. Many studies using cognitive testing find normal function in FM [148–157]. These negative results could truly define areas of normal function in these disorders or fail to detect dysfunction for a number of reasons [135]. Other studies have found deficits in attention, executive control, and working memory [146, 149, 155, 158–162]. These are usually associated with heavy task demands or during distraction; often no deficits are found for less demanding tasks [163]. However, these differences in objective performance appear to be of a small clinical magnitude and correlate poorly with subjective complaints of dyscognition [164].

In cases of equivalent performance, there is evidence that patients with fibromyalgia may "rise to the occasion" and perform at normal levels for the duration of the tests. The implication is that this high-level of performance can be achieved for a short period of time but not routinely maintained over longer periods of time. This hypothesis is supported by neuroimaging evidence that equal objective performance on cognitive tasks is associated with increased task-specific BOLD patterns in FM when compared to controls [163].

Neuroimaging Using Evoked Cognitive Testing Paradigms in Fibromyalgia

Glass (2011) used an fMRI response inhibition task in 18 FM and 14 controls [163]. Subjects performed a simple Go/No Go task that was assumed to be sufficiently lowdemanding to yield equivalent performance in the groups. The FM patients performed as well as the control subjects; there were no differences in performance between the two groups. However, there were differences in brain activity. FM had increased activity in the right inferior temporal gyrus/fusiform gyrus, suggesting increased task-related activation was required to achieve this equal performance. However, FM patients showed less activity

in a number of other structures, such as the SMA, PMC and attention networks (IPL, PMC, INS, VLPFC). These areas are often considered part of inhibition networks suspected to be required in proper stopping during the task [165]. There is considerable overlap between the inhibition networks and pain-related networks, with regions such as the ACC, MCC, and SMA participating in both networks. The investigators interpreted this reduced activity in the inhibition networks as reflecting reduced resources available for response inhibition due to the overlapping resources used by the pain network.

This initial study [163] was essentially repeated in the same subjects 12 weeks after the initial experiment [166]. The analysis identified patients who had a small improvement in widespread pain over time (as evaluated by body map) and showed an association between improvement and increased activity of response inhibition networks (dorsal ACC/MCC). The differences observed in these studies may dynamically reflect current FM symptom burden, although the clinical relevance of any such change is not clear.

Neuroimaging Using Evoked Cognitive Testing Paradigms in Chronic Fatigue Syndrome

Two small studies (n= 9, 19) compared performance of CFS patients to controls using a modified PASAT test, a complex auditory information processing task [167, 168]. CFS patients performed comparably to controls, an effort that was accompanied by increased activity in several cerebellar, temporal, cingulate, and frontal brain regions. In addition, as fatigue increased during a scanning session, the extent of brain activity increased in CFS patients compared to control subjects [167].

Neuroimaging Using Evoked Cognitive Testing Paradigms in Temporomandibular Joint Disorder

One study (n=17) measured performance during three STROOP tasks: using neutral words, using incongruent numbers, and using emotional words that included TMD-specific words. Performance, measured by reaction times, was slower in the TMD patients compared to controls and this poor performance was accompanied by generally increased evoked brain activity in all tasks [169].

Neuroimaging Using Evoked Cognitive Testing Paradigms in Irritable Bowel Syndrome

One study (n= 30) employed a standard Wisconsin Card Sorting Test (WCST) to assess task related brain activity [170]. The challenge of the task revolves around changes in the sorting rule, which requires repeatedly learning a new sorting rule and “forgetting” previous rules. IBS subjects had more errors that involved perseveration compared to controls and had concomitantly increased activity in the left pINS and decreased activity in the right DLPFC and HC. The functional network linking DLPFC and the pre-SMA in IBS also showed significantly increased activity in the left pINS during a rule change.

Neuroimaging Using Evoked Cognitive Testing Paradigms in Vulvodynia Syndrome

There have been no studies of cognitive functioning in VVS to date.

Brain Activity Evoked by Cognitive Tasks in “Central Sensitivity Syndromes”

After reviewing the entire literature, a consistent picture of the nature of cognitive dysfunction and dyscognition does not emerge. Small studies using a variety of cognitive paradigms are all able to demonstrate different patterns of increasing and decreasing BOLD activations. These results have been interpreted in a variety of ways, from competition between sensory and executive networks for resources to intrinsic impairment. However, the difficulties of demonstrating clinically meaningful objective differences in performance, the vast number of neurological processes that utilize the same anatomic areas, and the poor correlation of objective cognitive impairment with subjective dyscognition suggest that these pioneering efforts may not be accurately measuring dyscognition, the salient clinical issue of “central sensitivity syndromes”.

MULTIMODAL NEUROIMAGING OF THE EFFECT OF THERAPEUTIC INTERVENTION

As described above, the majority of the neuroimaging studies that have been performed to date have concerned themselves with taking measurements and making comparisons between a patient group and healthy controls. However, cross-sectional design cannot account for change over time, which limits the scope of questions that can be addressed. Prospective designs that seek to correlate changes in subjectively-reported clinical symptoms to objective neuroimaging correlates have the potential to provide important insights into these disorders. Typically, these studies follow a group of patients during the course of an intervention, taking measurements at a “baseline” time prior to therapy and again at the completion of therapy. The MRI data from these time points are then compared. If successful, prospective studies have the potential to elaborate the physiology responsible for symptoms and identify objective biomarkers for subjective experiences. Further, they could provide insight into the biologic mechanisms of current therapies, which could be “reverse-engineered” into a better understanding of the disorders. For these reasons, the most recent generation of neuroimaging studies, starting with Mayer in 2002 [171], are applying these methods to the study of “central sensitivity syndromes'. Compared to many of the studies described in this review, the neuroimaging analysis of longitudinal change is relatively new and the reviewed studies are often breaking new ground providing needed impetus while discovering new issues and factors to be considered. A comprehensive review of the literature using prospective interventional neuroimaging designs can be found in Table 5.

ISSUES WITH NEUROIMAGING OF TREATMENT EFFECT

Unfortunately, despite the aforementioned promise, a number of unique issues have emerged when applying the prospective interventional study design to neuroimaging. Some of these problems can be addressed in the study design; some are not addressable with current technology. These issues are reviewed here as they are essential to understanding the amount of uncertainty that needs to be considered when interpreting the results of prospective interventional neuroimaging studies.

ORDERING BIAS IN THE FUNCTIONAL IMAGING ENVIRONMENT

The experience of neuroimaging is uncomfortable for many people. The neuroimaging environment is claustrophobic and is often anxiety-provoking. Even in those able to tolerate the procedure, being in the neuroimaging environment itself has been shown to amplify sensations and impair performance on tasks compared to results obtained outside the scanner [172]. Problematically, the experience of that discomfort is implicitly measured in all functional neuroimaging studies. This is an important problem, as the neural networks that correlate with anxiety have substantial overlap with those of pain and other adverse symptoms. As with most experiences, the discomfort from the neuroimaging environment decreases over time, with concomitant change in neuronal activity. For some prospective treatment studies using functional imaging measurements, it becomes possible that the "treatment effect" seen with an intervention may be better explained by this ordering bias.

The Walitt (2007) study provides an example of this ordering bias [173]. The study employed a multimodal therapy in FM patients (n=9) that improved FIQ scores (0-100 scale) by 20.68 points (p=0.005), a moderate clinical improvement. Comparisons between pre-treatment and post-treatment 18-FDG PET scanning demonstrated that the patients had increased uptake in a number of cerebral regions considered to be part of the limbic system. The author concluded that a trend of increased metabolic activity in the limbic system was noted with symptomatic improvement in FM after treatment. However, as there was no functional task of pain sensitivity performed during the imaging, the measured brain activity best reflects the moment-to-moment experience of being in the PET scanner. It seems more likely that the neuroimaging changes represent a reduction in anxiety or discomfort with undergoing the scan than any specific treatment effect.

Ordering bias in the neuroimaging environment can be addressed by study design. The double-blind counterbalanced cross-over trial (DBPCCT), which has patients sequentially take both a placebo and a treatment, with half taking placebo first and the other half receiving treatment, is one method, although sensitivity is degraded in the presence of an order effect. Using subjective questionnaires to estimate the subjective MRI burden and consider it statistically in the analyses represents another potential method.

POST HOC FALLACY

Similar to ordering bias, the logical fallacy of *post hoc ergo propter hoc* ("After this, therefore because of this") is another inherent challenge to the interpretation of prospective neuroimaging studies. A key assumption made in intervention studies is that *any* change seen between the baseline measurement and the post-treatment measurement is caused by the specific intervention. For many health problems, this assumption is a valid one. The great majority of human physiological processes cannot be profoundly changed by lifestyle or agency.

Unfortunately for symptom science, both subjective symptoms and neurobiological activity are not independent from lifestyle and agency. The moment-to-moment state of a person's life is reflected in both. This makes it possible for non-treatment factors to play a causal role in the neuroimaging results. The natural history of these clinical disorders is that symptoms

substantially ebb and flow rather than remain static [174]. As it is most common for patients to enroll in research studies when their symptoms are particularly high, it is possible that much of any clinical improvements noted reflect “regression to the mean” rather than a discrete treatment effect [175]. Further, the act of participating in a trial and being studied may lead to symptomatic improvement that is not specific to any particular intervention. Other intangible factors can also play a role in clinical improvements, especially when the amount of improvement is small. For these reasons, the potential for misattribution of treatment effect in the neuroimaging is significant. Care must be taken when assuming that clinical improvements measured reflect the physiologic action of an intervention.

A study of acupuncture treatment in FM provides an example of a potential post hoc fallacy [176]. This study administered 9 sessions of acupuncture (n=5) or 9 sessions of sham acupuncture (n=5) and used MRS to measure Glu/Cr ratios in the right INS before and after therapy. A small clinical improvement in clinical pain rating (3.5 points on the 0–33 scale of the Short Form-McGill Pain Questionnaire) was demonstrated in both the active treatment and placebo groups. A similar minor improvement in pain sensitivity to blunt pressure testing (0.34kg improvement) was seen in both groups as well. The authors conclude that the alteration in pain reporting in the study patients was the cause of the correlation with insular Glu. However, considering the modest amount of clinical pain improvement reported, it is possible that other unaccounted-for factors, such as comfort or mood, may have played the causal role in the alterations in Glu reported.

It is very difficult to address the post hoc fallacy in the study design, as the number of intangible factors that can influence the results is vast and difficult to identify. Use of a placebo group and counterbalanced cross-over designs can potentially be helpful. Measuring potential confounders and adjusting for them in analyses is also beneficial.

MODEST TREATMENT EFFICACY

The clinical disorders addressed in this review are notoriously difficult to successfully treat. Currently, there are no treatments for any of these disorders that completely alleviate adverse symptoms. Rather, the efficacy of any of the treatments currently used is modest. The best studied interventions, such as the FDA-approved medications in FM, are only associated with a Minimal Clinically Important Difference (MCID) in clinical symptoms [177]. Therefore, every neuroimaging study of these clinical conditions describes mild improvement in symptoms rather than dramatic improvement. In many of the studies described below, the treatment effects described are only equivalent to that seen in a placebo group. The inability to make a self-evident improvement in symptoms undermines attempts to understand what a meaningful treatment effect actually is.

The problem of modest treatment efficacy is commonly masked with statistical language. For the reasons implicit in ordering bias and the post hoc fallacy, it is not difficult to demonstrate small differences in clinical symptoms over time. While the differences are often not clinically important, they are commonly statistically significant. The reporting of “significant” differences in pain reporting that are clinically irrelevant can be misleading.

A study of cognitive behavioral therapy (CBT) demonstrates the issue of modest treatment efficacy [178]. This study administered CBT to 19 FM patients with an open-label randomized controlled trial design that used a waiting list group as controls. BOLD activation related to pressure pain was measured before and after treatment. CBT led to increased pain-evoked activation of the VLPFC and OFC after treatment. However, the clinical meaning of those changes is not clear. The intervention was shown to lead to "minimal improvement" on the Patient Global Impression of Change ($p<0.01$) compared to controls but no differences in clinical pain ($p=0.26$) or pressure pain threshold measurements ($p=0.8$). The authors suggested that CBT changes the perception on clinical symptoms through an altered cerebral loop between afferent pain signals, emotions, and cognitions. Unfortunately, the inability to demonstrate clinically important improvement in symptoms with treatment undermines this interpretation.

Complicating the interpretation of treatment effect is the use of psychophysical testing as outcome measurements. Many of the paradigms mentioned previously are applied to the measurement of treatment effect, often being able to demonstrate statistical significance. Unlike subjective clinical reporting, there currently is no understanding of how changes in measures such as pressure-pain or thermal pain sensitivity translate into clinical meaningful distress. This issue is present in Petzke (2013) in which milnacipran was administered to 32 FM patients in a double-blind placebo controlled trial (DBPCT) [179]. The authors reported a 5.2mm±3.2mm downshift in the stimulus-response curve to pressure pain ($p=0.055$ one tailed) compared to placebo and described differences in pressure-pain BOLD activation patterns related to milnacipran therapy. However, the clinical relevance of a 5.2mm change in the stimulus-response curve is unclear and the authors did not provide any patient-reported outcome data to document a clinically-relevant treatment response. It is possible that the participants in this study did not have any meaningful treatment effect, a potential explanation for why no pre-post treatment differences were found in pressure-pain BOLD activity between the milnacipran and placebo groups.

Currently, it is not possible to address the issue of modest treatment efficacy. It is hopeful that future treatments will lead to self-evident improvements, which can then be used in these experiments.

SELECTION BIAS AND THE FALLACY OF INCOMPLETE EVIDENCE

Performing serial neuroimaging is both expensive and time-consuming, which often is a limiting factor in the number of patients who can be studied. Adverse treatment effects and participant attrition commonly lead to high drop-out rates. The significant attrition of study participants in studies that number from 10–25 participants reduces statistical power to the point that negates generalizing the results to the broader population. Further, many patients who do complete the studies do not gain any clinical benefits from the interventions. Many times these "non-responders" are not included in the analyses, further introducing selection bias into these studies. These issues often lead to the fallacy of incomplete evidence ("cherry picking") where only favorable data is used in the analysis and a significant portion of evidence is ignored that might contradict the findings.

A pharmacological study in FM demonstrates the fallacy of incomplete evidence [180]. The study recruited 21 FM patients to undergo treatment with pregabalin, measuring BOLD activity evoked by blunt pressure before and after treatment. Of the 21 participants, only 9 had a therapeutic response, with an additional 2 participants dropping out of the study prior to the final scan, leaving a final cohort of 7 patients. The study concluded that pregabalin influences aspects of pain-related networks, inducing longitudinal changes in neuronal activity during the pain state, and that it reduces pain and other core symptoms of FM. However, as the investigators did not consider the majority of their participants in the analyses, it is likely that these conclusions are not true for the majority of FM patients.

Addressing the fallacy of incomplete evidence is difficult. On the one hand, it is possible that there are multiple different mechanisms that lead to each of the clinical syndromes, the potential problem of physiological heterogeneity. If true, it would be expected that patients would respond to a therapy that targets their specific physiology while patients with a different physiological cause would not respond. From this point of view, investigating "responders" has potential value. However, discussing the nature of "responders" while ignoring "non-responders" can be deceptive, especially in the attempt to translate neuroimaging science into clinical practice.

REPLICATION AND STUDY POWER

No prospective interventional neuroimaging study has been independently replicated. While this is not a particular flaw of the prospective interventional neuroimaging design, it is particularly relevant when issues inherent in studies with small sample sizes, such as the Proteus Effect and the other aforementioned issues are all considered together [181]. It is likely that many of these studies are reporting larger effects due to random factors and that most will not be considered worth replicating by other investigative groups.

To the credit of the investigators attempting these complex studies, many are careful when interpreting their results. Some studies note that the results reflect the physiology of the treatment modality rather than a treatment effect "per se" [101]. Others use the clinical interventions as "probes" to investigate specific issues about the disorders rather than measure a specific treatment effect [182]. Others seek to use neuroimaging to "predict" response to a particular treatment. However, these nuanced considerations are often lost as scientists and clinicians seek to translate such neuroimaging results into hypothetical disease paradigms.

With the aforementioned caveats in mind, the next section reviews the reported neuroimaging alterations that are associated with therapeutic change in each of the clinical syndromes. Only studies that report findings about therapeutic change are discussed. Studies seeking to predict interventional effect or probe scientific questions not related to the treatment effect are not presented.

NEUROIMAGING THE TREATMENT EFFECT IN FIBROMYALGIA

Ten studies have reported neuroimaging correlates of treatment effects in FM. The first study (n=14) found that a 3-month course of amitriptyline was associated with increased

rCBF in bilateral thalamus [183]. FM patients (n=9) have also been shown to have an increase in a PET surrogate for brain metabolism in 13 pain-related regions after a median improvement in the FIQ of 20.7 (p=0.005) [173]. FM patients who had a >50% decrease in pain VAS scores after ketamine treatment (n=11) showed increased rCBF by SPECT in the midbrain, while in non-responders (n=6) midbrain rCBF decreased [184]. Three studies of the same cohort used acupuncture to measure treatment effect [176, 185, 186]. No difference in therapeutic effect was noted between the acupuncture and sham acupuncture interventions. The treatment groups were combined together in the analyses, with average clinical improvement on the short form McGill Pain Questionnaire in these studies approximating 3.5 (p=0.05). These studies report correlation between clinical pain and Glu/Cr ratio in the pINS (n=10; r=0.85, p=0.002), increased μ-opioid binding potential (as measured by ^{11}C-carfentanil PET) in 10 pain-related regions (n=20), and reduced connectivity between the DMN and right INS and right putamen (n=17) after treatment. One study using behavioral extinction therapy (n=10) was able to demonstrate an increase in pellet-pain tolerance ($p<0.05$) and Multidimensional Pain Inventory (MPI) pain intensity ($p<0.05$) but not MPI pain sensitivity [101]. This treatment effect correlated with increased BOLD activity to pellet-pain stimulation in the pINS and contralateral S1. An open-label study of routine clinical treatment with pregabalin compared the pain evoked BOLD activity of responders (n=9) to that of non-responders (n=10) [180]. Responders had increased BOLD activity in the bilateral fusiform, ipsilateral IPL, and contralateral superior TC. Two studies used the same DBPCT cohort (n=30, 32) to measure the effects of milnacipran therapy on pressure-pain BOLD activity [179, 187]. The first study did not report any patient reported outcome measurements but demonstrated a 5.2mm downshift trend in the stimulus-response curve to pressure pain stimulation compared to placebo (p=0.055 one-tailed). Increased pain evoked BOLD activity was noted after treatment with milnacipran in multiple pain-related regions. However, no differences in BOLD changes were noted between milnacipran and placebo. The second study segregated participants into milnacipran responders (n=21) and placebo responders (n=16) based on reporting minimal improvement or greater on the Patient Global Impression of Change. Combining milnacipran and placebo responders into a single responder group demonstrated increased bilateral AMY BOLD activity to pressure pain.

When taken together, a coherent picture of the treatment effect of FM does not appear. Measurements of the treatment effect on pressure-pain sensitivity appear counter-intuitive, with increases seen in BOLD activity. No study demonstrated decreases in evoked BOLD activity with treatment, as would be expected with `normalization' of central amplification of peripheral stimulation. Also, brain regions in which evoked BOLD activity are increased are often related to pain but are anatomically inconsistent between the studies. Brain metabolic activity was shown both to increase and decrease with treatment. Evidence for alterations with therapy in μ-opioid binding measured with PET and Glu measured with MRS do exist but are based on marginal clinical improvements in underpowered cohorts. The ability to measure treatment effects meaningfully in FM has not been successfully demonstrated.

NEUROIMAGING THE TREATMENT EFFECT OF IRRITABLE BOWEL SYNDROME

While 8 studies used treatment in fMRI of IBS, only 3 were focused on determining a treatment effect. One was a three week DBPCT of alosetron (n=20) in which treatment led to improvement in current abdominal pain and rectal distention evoked discomfort (>50% change on figure, $p<0.05$). Increase in ^{15}O-water PET activity with treatment were found in the left INS, frontotemporal cortices, and the cuneus with concomitant decreases seen in the bilateral AMY, ACC, medial OFC, and right posterior superior TC. However, similar results were also demonstrated in the placebo group [171]. The second was a 4-week DBPCT of amitriptyline. Patient-reported outcome scores were not provided but no difference was seen between amitriptyline and placebo on abdominal pain VAS ($p=0.2$) or rectal distention discomfort ($p=0.1$). Decreased BOLD activation with rectal distention was noted with amitriptyline use in the ACC and left PPC. However, no comparison in BOLD activity between the amitriptyline and placebo group was reported [188]. The third study compared hypnotherapy responders (n=13) to educational therapy responders (n=7). Both groups of responders had >50 point changes in the IBS-Symptom Severity Scale. All responders had reduced rectal distention evoked BOLD activity in the INS, VLPFC, AMY, and HC [189].

These results do not provide a coherent or meaningful picture of the treatment effect in IBS.

NEUROIMAGING THE TREATMENT EFFECT IN TEMPOROMANDIBULAR DISORDER

Only one rs-FMRI study has investigated the treatment effect in TMD using a stabilization splint (n=11) [190]. Improvements in the Helkimo index was demonstrated prior to treatment (1.7 points, $p=0.02$) and after treatment (7.8, $p=0.06$) but no changes were noted in characteristic pain intensity. After three months of treatment, increases in the fractional amplitude of low frequency fluctuations in resting state were noted in the left M1 and left pINS.

This result does not provide a coherent or meaningful picture of the treatment effect in TMD.

NEUROIMAGING THE TREATMENT EFFECT OF CHRONIC FATIGUE SYNDROME

Only one study has investigated the treatment effect in CFS using CBT (n=22) [52]. The intervention led to improvements in the fatigue measured by a subscale of the Checklist Individual Strength of −19 ($p<0.001$) and Sickness Impact Profile of −784 ($p<0.001$). An increase in whole brain GM volume was noted with treatment ($p=0.03$), in particular the bilateral VLPFC.

This result does not provide a coherent or meaningful picture of the treatment effect in CFS.

NEUROIMAGING THE TREATMENT EFFECT IN VULVODYNIA

There are no studies of the treatment effect in VVS.

NEUROIMAGING OF TREATMENT EFFECTS IN "CENTRAL SENSITIVITY SYNDROMES"

Despite pioneering efforts from clinical scientists, the ability to image the treatment effect in these clinical syndromes remains in its infancy. Major technical and logical obstacles will need to be overcome before a coherent and clinically relevant picture of the neuroimaging correlates of treatment emerges.

EMERGING IMAGING TECHNIQUES

Novel imaging methods continue to be developed that may provide insight into "central sensitivity syndromes". The role of the spinal cord in these disorders is of great interest, as the dorsal horn is the first "port of call" for incoming nociceptive signaling from peripheral nerves. Functional techniques have been recently adapted to the spinal cord. Spinal cord imaging is more technically complicated than brain imaging due to the small cross-sectional dimension of the spinal cord, cardio-respiratory motion, and magnetic susceptibility differences between spinal laminae and spinal neurons [191]. Spinal fMRI has been able to demonstrate signal intensity changes during both innocuous and noxious thermal stimulation [192]. However, spinal fMRI has not yet been applied to "central sensitivity syndromes".

The contributions of non-neuronal cells within the CNS, in particular glial cells, to the experience of pain have also been an area of recent interest. Recently, techniques to image the metabolic activity of glial cells has been developed. Estimates of glial activity can be made using PET imaging of a ligand of translocator protein (TPSO), a mitochondrial protein with roles in cholesterol transport and inflammation that is only minimally expressed in brain tissue [193]. One recent study reported increased TPSO binding by PET in the TH and areas of S1 in patients with chronic low back pain compared to controls carefully matched based on TSPO gene polymorphisms (n=9) [194]. However, such techniques have not been applied to other "central sensitivity syndromes" to date.

CONCLUSION

Neuroimaging has been applied to the study of "central sensitivity syndromes" for nearly three decades. A large amount of data has been collected, but mostly from small heterogeneous studies rather than large, well-powered cohorts. It is likely that many of the aforementioned results would fail to persist if challenged with larger sample sizes or independent replication.

All of the methods applied above demonstrate differences between patients with clinical disorders when compared to healthy controls, an appropriate comparison for disease states. However, epidemiological evidence demonstrates that these disorders do not appear to be discrete diseases. Rather, they appear to represent dimensional or continuum disorders [195, 196]. Viewed from a spectral perspective, the entire body of neuroimaging research to date

focuses only on comparing the extreme ends of a somatic experience that is distributed throughout the population. Comparisons of the extremes of distributions have the attendant propensity to detect minor and often irrelevant abnormalities. The numbers of these minor findings increase proportionally to the amount of studies and the numbers of tests being performed across such studies. Rather than providing meaningful insight into the nature of these disorders, the results are often transformed into hypothesis-generating exercises or presented as yet more evidence that these clinical syndromes have neurobiological correlates. Even those studies whose results hold up in larger replication studies may be irrelevant to the causality of “central sensitivity syndromes”. Very few neuroimaging studies ever report major, field transforming findings.

Despite these serious issues, neuroimaging has made important contributions to our understanding of “central sensitivity syndromes”. The biological response to painful stimuli has been shown to increase in a scalable fashion in many of these disorders, demonstrating that a portion of the symptom burden is based in unconscious reflexive physiological mechanisms. This is a transformative observation for illnesses historically considered to be completely of hysterical or feigned in origin. Other observations, such as chronic pain being associated with altered DMN dynamics [197] and that robust improvements in chronic pain lead to predictable neurological alterations [198, 199], also appear to be important contributions. It is likely that continuing neuroimaging innovation will provide new, important, and exciting insights into how our bodies create disturbing sensations.

However, the current literature has its explanatory limits. All the reviewed neuroimaging results document effects, the biological correlates that are related to an evoked sensation, prompted behavior, or diagnostic state. Logically, effects themselves cannot describe their antecedent causes. In this way, pain augmentation represents a response rather than a cause. At this time, the neuroimaging literature does not support “central sensitization” as a cause of these syndromes but suggests that “central sensory augmentation” is either a predisposing factor or a consequent effect.

Lastly, the concept that “central sensitivity syndromes” are biologically-related entities is not strongly supported by the sum of the neuroimaging evidence. Some passing similarities are noted, but are far outweighed by heterogeneity and inconsistency when results are compared between disorders. At this time, there is substantially more clinical evidence that “central sensitivity syndromes” are related than exists scientifically. A coherent picture of a “central sensitization” mechanism that bridges across all of these syndromes does not emerge from the existing scientific evidence.

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Biography


Brian Walitt

LIST OF ABBREVIATIONS

Syndromes

CFS	Chronic Fatigue Syndrome
FM	Fibromyalgia
IBS	Irritable Bowel Syndrome
TMD	Temporomandibular Joint Disorder
VVS	Vulvodynia Syndrome

Brain Regions

ACC	Anterior Cingulate Cortex
aINS	Anterior Insula
AMY	Amygdala
CC	Cingulate Cortex
DLPFC	Dorsolateral Prefrontal Cortex
HC	Hippocampus
GP	Globus Pallidus
INS	Insula
M1	Primary Motor Cortex
MCC	Middle Cingulate Cortex
mINS	Middle Insula
MPFC	Medial Prefrontal Cortex
OFC	Orbitofrontal Cortex
PAG	Periaqueductal Gray
PCC	Posterior Cingulate Cortex
PFC	Prefrontal Cortex
PHG	Parahippocampal Gyurs

pINS	Posterior Insula
PMC	Premotor Cortex
PPC	Posterior Parietal Cortex
S1	Primary Somatosensory Cortex
S2	Secondary Somatosensory Cortex
SMA	Supplementary Motor Area
SPL	Superior Parietal Lobule
IPL	Inferior Parietal Lobule
TC	Temporal Cortex
TH	Thalamus
VLPFC	Ventrolateral Prefrontal Cortex

Imaging Methods and Measures/Outcomes

AD	Axial Diffusivity
ASL	Arterial Spin Labeling
BOLD	Blood Oxygenation Level Dependent
CBF	Cerebral Blood Flow
Cho	Choline
Cr	Creatine
CTA	Cortical Thickness Analysis
DTI	Diffusion-Tensor Imaging
FA	Fractional Anisotropy
fALFF	Fractional Amplitude of Low Frequency Fluctuations (in resting-state fMRI)
FDG	18F- fluorodeoxyglucose
fMRI	Functional Magnetic Resonance Imaging
Glu/Cr	Glutamate/Creatine ratio
Glx	Glutamate/Glutamine
GM	Gray Matter
HF	High Frequency
H-MRS	Proton Magnetic Resonance Spectroscopy
ICA	Independent Component Analysis
LF	Low Frequency

MD	Mean Diffusivity
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NAA	N-Acetylaspartate
PET	Positron Emission Tomography
rCBF	Regional Cerebral Blood Flow
RD	Radial Diffusivity
Rs-fMRI	Resting State Functional MRI
Rs-FC	Resting State Functional Connectivity
SPECT	single photon
TR	Repetition Time (in fMRI)
VBM	Voxel-Based Morphometry
WM	White Matter

Treatments and Behavioral Measures/Outcomes

ACU	Acupuncture
BPI	Brief Pain Inventory
CBT	Cognitive Behavioral Therapy
DBPCCT	Double-Blind Placebo Controlled Counterbalanced Crossover Trial
FIQ	Fibromyalgia Impact Questionnaire
FS-CIS	Fatigue Subscale of the Checklist Individual Strength
MCID	Minimal Clinically Important Difference
MLN	Milnacipran
MPI	Multidimensional Pain Inventory
PBO	Placebo
PGIC	Patient Global Impression of Change
SBPCT	Double-Blind Placebo Controlled Trial
SIP	Sickness Impact Profile
SRT	Simple Reaction Time
SF-MPQ	Short Form McGill Pain Questionnaire
STAI	State Trait Anxiety Inventory
SSS	Somatic Severity Score

Tx	Treatment
VAS	Visual Analog Scale
PANAS	Positive and Negative Affect Schedule

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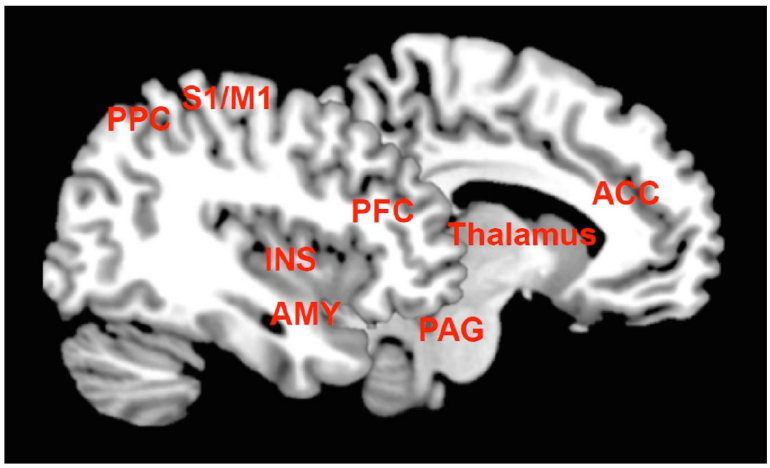

Fig. (1).
Anatomic areas that are part of “Pain-Related Networks”.

Table 1

Summary of basal metabolic activity of the brain in central sensitivity syndromes.

Technique	Disorder	Study	Patients Sex, n	Increase	Decrease
SPECT	FM	Mountz, 1995	F, 10	None	TH(r,l), Caudate Nucleus(r,l)
	FM	Kwiatek, 2000	F, 17	None	TH(r)
	CFS	Schwartz, 1994	F, 29 M, 16	rCBF: Lateral frontal, temporal cortex and basal ganglia	None
	CFS	Ichise, 1992	60	None	rCBF: Frontal, temporal, parietal, and occipital cortices and basal ganglia
	CFS	Fischler, 1996	F, 14 M, 2	None	None
	CFS	Lewis, 2004	F, 20 M, 2	None	None
	CFS	Lewis, 2001	11 monozygotic twin pairs	None	None
PET	FM	Wik, 2003	F, 8	rCBF: Retrosplenial cortex(r,l)	None
	FM	Yunus, 2004	F, 12	None	None
Xenon CT	CFS	Yoshiuchi, 2006	F, 18 M, 7	None	rCBF: Middle cerebral arteries(r,l)
fMRI	FM	Napadow, 2010	F, 18	Rs-FC: between the DMN seed and EAN(r), and INS.	None
	FM	Kim, 2013	F, 19	PSD: S1(r,l), SMA(r,l), DLPFC(r,l) and AMY(r,l)	None
fMRI	IBS	Hong, 2013	F, 31 M, 29	M: HF power distribution in aINS(l), mINS(r,l), and pINS(l). F: HF, MF power distribution in AMY(l), HIPP(r), and aINS(r,l)	None
	TMJ	Ichesco, 2012	F, 8	Rs-FC: aINS(l) and ACC(l); pINS(l) and PHG; aINS(r) and TH(r)	None
	TMJ	Kucyi, 2014	F, 17	Rs-fC: mPFC seed, PCC, and retrosplenial cortex	None
Perfusion-MRI	FM	Foerster, 2011	F, 17 M, F	None	None
ASL	CFS	Biswal, 2011	11	None	Global CBF
	TMJ	Yousseff	F, 12 M, 3	rCBF: Cerebellum(r), PMC(r), ACC, pINS(l), GP(l), precuneus	None

Table 2

Summary of structural gray matter alterations in central sensitivity syndromes.

Disorder	Study	Patients Sex, n	GM increase (VBM, CTA)	GM reduction (VBM, CTA)
FM	Jensen, 2013	F, 26	Superior parietal (r)	Cortical GM, subcortical GM, rACC (l), DLPFC (l), OFC (r,l), AMY (r), TC (r), fusiform (r)
	Ceko, 2013[a]	F, 14 (age>50)	None	ACC/MPFC (r,l) PMC (r), temporooccipital (r), PCC/SMA (r), VLPFC (l), DLPFC (l)
	Ceko, 2013	F, 14 (age<50)	aINS (r,l), mINS (l), putamen (r,l), GP (r), nucleus accumbens (r), VLPFC (r)	None
	Fallon, 2013	F, 16	S1 (r,l)	Brainstem (l), precuneus (l)
	Robinson, 2011	F, 14	None	mINS (l), dorsal ACC (l), rostral ACC (l)
	Hsu, 2009	F, 29 (with affective disorder)	None	aINS (l); *no GM differences in a different sample of FM (n=29) without affective disorder*
	Burgmer, 2009	F, 14	None	ACC (r), AMY (r), lateral PFC
	Wood, 2009	F, 30	None	PHG (r,l), ACC (l), PCC (r)
	Lutz, 2008	F, 30	None	HC (r,l)
	Schmidt-Wilcke, 2007	M, 1 F, 19	BG (r, l), OFC (l), Cerebellum (l);	TC (r), thalamus (l); *additionally in ACC (r,l), INS (l),TC (l), medial parietal*
	Kuchinad, 2007	F, 10	None	Total GM, INS (l), MPFC, PHG (l), PCC
CFS	Puri, 2012	M, 7 F, 19	None	Occipital (r,l), angular gyrus (r), PHG (l)
	De Lange, 2008	F, 22	None	Total GM; no regional differences
	De Lange, 2005	F, 28	None	Total GM; no regional differences
	Barnden, 2011	F, 19 M, 6	None	None
	Okada, 2004	F, 28	None	DLPFC (r)
IBS	Labus, 2014	F, 82	S1 (l)	DLPFC (r,l), INS (r,l), AMY (r,l), HC (r,l), OFC (r,l), cingulate (l), gyrus rectus (l), brainstem, putamen (l)
	Hong, 2014	M, 2 F, 9	None	Decreased cortical thickness: aINS (r)
	Jiang, 2013	F, 70	S1/M1 (r,l)	Decreased cortical thickness: sgACC (r,l), aINS (l), mINS (r), pINS (r,l)
	Piche, 2013	F, 14	m/pINS	None
	Seminowicz, 2010	F, 56	pACC (l), OFC (l); HC/PHG (r,l), S2/pINS (r) DLPFC (l)	PPC (l), precuneus (l), TC (r,l), VLPFC (r,l), MPFC (l), PMC (l), frontal pole (l), thalamus (r,l), ventral striatum (r,l), occipital (l)
	Blankstein, 2010	F, 11	Hypothalamus	Cortical thinning: aMCC
TMD	Gerstner, 2011	F, 9	None	ACC (l), PCC (r), aINS (r), VLPFC (l), TC (r,l)
	Moayedi, 2011	F, 17	Incrased cortical thickness: S1 (r), frontal pole (l), VLPFC (l)	None
	Younger, 2010	F, 15	VLPFC (r), aINS (r), putamen (r), thalamus (r,l), GP (r), pons (r,l)	S1

Disorder	Study	Patients Sex, n	GM increase (VBM, CTA)	GM reduction (VBM, CTA)
	Davis, 2008	M, 3 F, 6	None	Thalamus, ACC; Cortical thinning: dACC (r), aINS (r,l)
VVS	Schweinhardt, 2008	F, 14	HC (l), PHG (r), basal ganglia (l)	None

[a]Combined sample: F, 28, GM reductions in ACC/MPFC (r, l), PMC (r), DLFPC (l); no regions of increased GM

Table 3

Summary of structural white matter alterations in central sensitivity syndromes.

Disorder	Study	Sex, n	WM alterations ↓↑
FM	Kim, 2014	F, 19	↓ FA, ↑ RD, ↓ AD: corpus callosum adjacent to ACC (l)
	Jensen, 2013	F, 26	↓ Total cortical WM
	Ceko 2013	F, 14 (age>50)	↓ FA, ↑ RD, ↓ AD: corpus callosum adjacent to PCC (r)
	Ceko 2013	F, 14 (age<50)	↑ FA, ↓ RD, ↓ MD: anterior thalamic radiation/anterior limb of internal capsule medial to putamen (l)
	Sundgren 2007	F, 16 M, 3	↓ FA thalamus (r)
	Lutz 2008	F, 30	↑ FA in ACC (r,l), dorsal PFC (r,l); ↓ FA in thalamocortical tract (r,l)
CFS	Puri 2012	F, 19 M, 7	↓ WM volume in occipital lobe (l)
	Okada 2004	F, 6 M, 10	No differences
IBS	Chen 2011	F, 10	↑ FA: fornix, external/extreme capsule adjacent to INS (r)
	Ellingson 2013	F, 21 M, 12	↓ FA thalamus, basal ganglia, sensory-motor areas, and PCC ↑ FA MPFC and corpus callosum
TMD	Gerstner 2011	F, 9	↓ WM volume MPFC (r,l), ACC (r,l) DLPFC (r,l), precuneus (l), VLPFC (l), ↑ WM volume: TC (r,l)
	Moayedi 2012	F, 17	↓ whole brain FA, ↓ FA, ↑ RD, ↑ MD : internal capsule (r), external/extreme capsule adjacent to INS (r), adjacent to VLPFC (r), adjacent to S1/M1, corpus callosum (r,l), thalamus (r,l) ↓ WM connectivity between genu corpus callosum and DLPFC, ↑ WM connectivity between corpus callosum and frontal pole

Table 4

Summary of molecular alterations in central sensitivity syndromes.

Technique	Disorder	Study	Gender, n	Increase	Decrease
H-MRS	FM	Petrou, 2008	F, 17 M, 4	none in BG	none in BG
	FM	Emad, 2009	F, 15	Cho in HIPP(r)	NAA in HIPP(r,l)
	FM	Wood, 2009	F, 16	None	NAA:Cr in HIPP(r)
	FM	Harris, 2009	F, 19	Glu, Glx in pINS(r)	None
	FM	Fayed, 2010	F, 9 M, 2	Glx in PCC	Ins* in HIPP(r,l), Ins:Cr in SMA(l), HIPP(l)
	FM	Valdes, 2010	F, 28	Glx in AMY(r)	None
	FM	Feraco, 2011	F, 11 M, 1	Glx:Cr in VLPFC(r,l)	None
	FM	Foerster, 2012	F, 16	None	GABA in aINS(r)
	FM	Fayed, 2012	F, 9 M, 1	Glx in PCC	None
PET	FM	Harris, 2007	F, 17	Mu-opoid BP in NA, AMY, dorsal CC	None
	FM	Wood, 2007	F, 7	FDOPA uptake in TH(r,l), ACC(r,l), SN(r,l) and HIPP(r,l)	None
H-MRS	CFS	Chaudhurri, 2002	F, 7 M, 1	Cho:CR in BG	None
	CFS	Puri, 2002	F, 6 M, 2	Cho:Cr in occipital cortex	None
	IBS	Niddam, 2011	F, 8 M, 7	None	Glx in HIPP(r,l)
	TMD	Gestner, 2012	11	Gln: INS (r), NAA, Cho: INS (l)	None

Table 5

Summary of neuroimaging alterations associated with a “treatment effect”.

Author (Year)	n	Study Design	Treatment	Treatment Effect	Neuroimaging Technique and Findings	Design Problems
FMS						
Schmidt-Wilcke (2014)	Enrolled: 23 Included: 15	DBPCCT	Milnacipran 6 weeks	BPI S: −0.88±1.8 (0.08) BPI I: −1.1±1.7(0.03) No difference in BPI compared to PBO (p=0.78, p=0.31)	Default Mode Network Connectivity before and after both Txs: ◦Reduced connectivity between rACC and INS, PAG and INS predict Tx response	Post-Hoc No MCID Prediction Only Not Replicated
Diers (2012)	Enrolled: 10 Included: 10	Open-Label	Behavioral Extinction 12 weeks	MPI S: <MCID, (p=NS)* MPI I: <MCID, (p<0.05)* Increase in Repetitive Pellet-Induced Pain Tolerance (p<0.05)	Evoked Pain BOLD activity before and after Tx: ◦Tx increased BOLD in pINS and contralateral S1 ◦No significant difference in pre-post contrast evoked BOLD signal	Ordering Bias No Controls Post-Hoc No MCID Not Replicated
Kim (2013)	Enrolled:21 Responders: 9 Nonresponders: 12 Included: 7	Open-Label	Routine clinical treatment with Pregabalin Length Unspecified	FIQ: −37.47 (p<0.001) Increase in Pressure Pain Threshold: 0.82 (p<0.01)	Evoked Pain BOLD activity before and after Tx: ◦Responders had increased BOLD in bilateral fusiform, ipsilateral IPL, and contralateral superior TC	Low Power No Placebo Ordering Bias Post-Hoc Cherry-Picking Not Replicated
Harris ■ (2009)	Enrolled ACU: 10 Enrolled Sham ACU: 10	SBPCT	9 acupuncture (ACU)/sham ACU sessions over 1 month	SF-MPQ: −3.45±7.39 (p<0.05) No difference in SF-MPQ scores compared to sham acupuncture	^{11}C-carfentanil PET measurement of μ-opioid binding before and after Tx. Tx and sham groups combined in analysis. ◦During 1st Tx: 14 regions including pain-related regions ◦Tx Effect: 10 regions including pain-related regions ◦Correlation between SFMPQ and	Probe Ordering Bias Post-Hoc No MCID Combined Placebo Not Replicated

Author (Year)	n	Study Design	Treatment	Treatment Effect	Neuroimaging Technique and Findings	Design Problems
					PET in acupuncture subgroup: 7 regions with negative correlation	
Harris [■] (2008)	Enrolled ACU: 5 Enrolled Sham ACU: 5	SBPCT	9 acupuncture (ACU) or 9 sham ACU sessions over 1 month	SF-MPQ: −3.50±4.70 (p=0.05) No difference in SF-MPQ scores compared to sham acupuncture Increase in Pressure Pain Threshold: −0.34kg (p=0.05)	H-MRS before and after Tx: Treatment and sham groups combined in analysis. ◦Positive correlation with Tx and Glu/Cr in pINS (r=−0.85, p=0.002) ◦Negative correlation with pressure pain and Glu/Cr in pINS (r=−0.95, p<0.001) ◦Changes in Glu/Cr in right pINS correlate with BOLD changes in left pINS during pressure pain.	Low Power Ordering Bias Post-Hoc No MCID Combined Placebo Not Replicated
Jensen (2012)	Enrolled CBT: 25 Complete CBT: 19 Enrolled No Tx: 18 Complete No Tx: 15	Open-label RCT	Cognitive Behavioral Therapy (CBT) 12 weeks	◦PGIC: “minimally improved” (p<0.01) ◦Pain VAS: No group difference (p=0.26) ◦STAI-State: CBT improvement (p=0.04) ◦Pressure Pain Thresholds: No group difference (p=0.8)	Pressure pain BOLD activity before and after Tx: ◦Correlation between STAI-State and VLPFC activation Increased VLPFC-thalamic connectivity in CBT compared to No Tx.	Ordering Bias Post-Hoc No MCID Not Replicated
Petzke [■] (2013)	Enrolled MLN: 46 Complete MLN: 32 Enrolled PBO: 46 Complete PBO: 38	DBPCT	Milnacipran (MLN) 13 weeks	◦No clinical pain measure reported ◦Stimulus-response curve: 5.2mm±3.2mm downshift in MLN compared to PBO (p=0.055 one-tailed)	Pressure Pain BOLD Activity before and after Tx: ◦MLN treatment increased BOLD in 9 pain-related regions ◦PBO treatment had BOLD change in parietal cortex and INS ◦No pre-post differences in BOLD between MLN and PBO	Post-Hoc No MCID Not Replicated

Author (Year)	n	Study Design	Treatment	Treatment Effect	Neuroimaging Technique and Findings	Design Problems
Jensen[■] (2014)	Enrolled MLN: 46 Complete MLN: 30 MLN Responders: 21 Enrolled PBO: 46 Complete PBO: 30 PBO Responders: 16	DBPCT	Milnacipran (MLN) 12 weeks	◦PGIC: "Any improvement" used as responder criteria ◦Pain VAS and FIQ collected but results not reported ◦p50 pressure pain improvement in MLN responders compared to PBO responders ($p<0.05$)	Pressure Pain BOLD Activity before and after Tx: ◦No baseline difference between MLN and PBO responders ◦Increased PCC in MLN responders ◦Increased bilateral AMY in both MLN and PBO responders	Post-Hoc Unclear MCID Cherry-Picking Combined Placebo Not Replicated
Walitt (2007)	Enrolled: 12 Complete: 9	Open-label	Multimodal Therapy 8 weeks	◦FIQ: median improvement 20.7 ($p=0.005$) ◦Tender points: median decrease of 4 points ($p=0.02$)	^{18}FDG-PET Activity before and after Tx: ◦Post-treatment increase in FDG uptake in 13 pain-related regions	Low Power No Placebo Ordering Bias Post-Hoc Not Replicated
Hunter (2009)	Enrolled DLX: 6 Complete DLX: 5 Respond DLX: 2 Enrolled PBO: 6 Complete PBO: 2 Respond PBO: 0	DBPCT	Duloxetine (DLX) 12 weeks	◦BPI: ◦Response criteria based on BPI and PGIC.	Quantitative EEG at baseline and after 1 week of Tx: ◦LF Cordance changes at baseline correlated with BPI response but not PGIC response. ◦LF Cordance changes at 1 week predicted BPI and PGIC response at 12 weeks ◦No comparison to placebo results	Low Power Prediction Only Post-Hoc Cherry-Picking Not Replicated
Guedj (2007)[‡]	Enrolled: 17 Responders: 11 Nonresponders: 6	Open-label	Ketamine SQ 10 days	◦Responder was ≥50% decrease in pain intensity VAS	ECD-SPECT Activity before and 2 weeks after Tx completion: ◦Pre-treatment midbrain rCBF was increased in responders ($p=0.02$) ◦Post-treatment midbrain rCBF increased after treatment in responders ($p=0.02$) † and decreased in non-responders ($p=0.01$) † ◦% change in VAS correlated	Ordering Bias No Placebo Post-Hoc Cherry-Picking Not Replicated

Author (Year)	n	Study Design	Treatment	Treatment Effect	Neuroimaging Technique and Findings	Design Problems
					with midbrain rCBF after Tx (r=0.7, p=0.004)	
Napadow[■] (2012)	Enrolled: 17 ◦Both interventional groups combined in analyses	SBPCT	9 acupuncture (ACU)/sham ACU sessions 1 month	◦SF-MPQ sensory: −4.7 (p=0.02) ◦SF-MPQ affective: −0.9 (p=0.09)	Resting State fMRI before and after Tx: Tx and sham groups combined in analysis. ◦Reduced connectivity between DMN and right INS and right Putamen ◦Reduced SF-MPQ positive correlation with DMN and lelft aINS and left AMY	Probe Ordering Bias Post-Hoc No MCID Combined Placebo Not Replicated
Usui (2010)	Enrolled FM: 35 Complete FM: 29 Responder FM: 16 Nonresponder FM: 13 Controls: 10	Open-label	Gabapentin 5 weeks	◦Responder was ≥50% decrease in pain intensity VAS	ECD-SPECT before Tx: ◦Nonresponders had increased rCBF in right middle TC, left DLPFC, right precuneus, right ACC, left middle occipital cortex, left cerebellum	Ordering Bias No Placebo Post-Hoc Cherry-Picking Not Replicated
CFS						
De Lange (2008)	Enrolled CFS: 29 Complete CFS: 22 Controls: 22	Open-label	CFS: CBT 6–9 months Controls: No treatment	◦FS-CIS (8–56): −19 (p<0.001) ◦SIP (0–9937): −784 (p=<0.001) ◦Actigraphy: no Tx difference (p=0.06) ◦SRT: No Tx difference (p=0.14)	Grey Matter Volume measurements before and after Tx: ◦No prospective change in GMV in controls ◦Prospective increase in whole brain GMV in CFS (p=0.03), bilateral lateral PFC ◦Increase in GMV in CFS compared to controls (p=0.04)	Post-Hoc Unclear MCID Non-treated control group Not Replicated
TMD						

Author (Year)	n	Study Design	Treatment	Treatment Effect	Neuroimaging Technique and Findings	Design Problems
He (2014)	Enrolled TMD: 23 Complete TMD: 11 Control: 20	Open-label	Stabilization Splint 3 months	◦Helkimo index: Improved 1.73 between screening visit and start of treatment (p=0.02) ◦ Improved 7.8 between screening visit and end of treatment (p<0.001) ◦No reporting of changes in Characteristic Pain Intensity	Fractional Amplitude of Low Frequency Fluctuations in resting state before and after Tx: ◦Increased fALFF in left M1 and left pINS ◦Normalization of fALFF compared to controls in left SMA, left MFG, and right OFC ◦Decreased fALFF in left S1 and right SPL	Post-Hoc Cherry-Picking Not Replicated
IBS						
Hubbard (2011)	Enrolled IBS: 14 Enrolled Controls: 17	DBPCCT (3xCross-over)	GW876008 (2 doses) Single Dose	◦PANAS Subscales: No treatment effect ◦STAI state and traits scales: No treatment effect	Pain expectation paradigm BOLD related changes before and after Tx: ◦Reduction of BOLD in left ACC, OFC, pINS, and HC	Probe Post-Hoc No MCID Not Replicated
Letzen (2013)	Enrolled IBS: 11	DBPCCT	Rectal Lidocaine Single Dose	◦Pain VAS (0-100) to rectal distention: Improved by 15.5 (p<0.05)	Rectal Distention BOLD measurements before and after TX: ◦Decreased spatial extent of DMN in INS and M1 ◦Alteration of interactions between DMN and pain-related networks	Probe Not Replicated
Chu (2012)	Enrolled ACU: 15 Sham ACU: 15	SBPCT	Electo-acupuncture Single Tx	◦Rectal Distention VAS: No difference between Tx	Rectal Distention BOLD measurements before, during, and after Tx ◦Widespread differences in BOLD pattern seen between groups during and after Tx	Probe Post-Hoc No MCID Not Replicated

Author (Year)	n	Study Design	Treatment	Treatment Effect	Neuroimaging Technique and Findings	Design Problems
Lowen (2013)	Enrolled: 44 Enrolled HypTx: 25 Complete HypTx: 16 Responder HypTx: 13 Enrolled EdTx: 16 Complete EdTx: 9 Responder EdTx: 7 Controls: 18	Open-label	Hypnosis (HypTx) or Education (EdTx) 7 weeks	◦IBS SSS: Responder: 50 point change HypnoTx: 109 ($p<0.0001$) Education: 84 ($p=0.02$) No statistical difference between Tx.	Rectal Distention BOLD measurements before and after Tx: ◦Decrease BOLD in aINS, VLPFC, AMY, HC, and pINS ◦Normalization of BOLD in VLPFC, ACC compared to controls	Ordering Bias Post-Hoc Cherry-Picking Not Replicated
Mayer (2002)	Enrolled: 52 Randomized: 47 Complete Alosetron: 20 Complete PBO: 17	DBPCT	Alosetron 3 weeks	◦ Current abdominal pain VAS: Improvement >MCID ($p<0.05$)* ◦ Rectal Distention VAS: Improvement >MCID ($p<0.05$)*	^{15}O-water PET before and after Tx: ◦Post Tx PET increase in left INS frontotemporal, and cuneus ◦Post Tx PET decrease in bilateral AMY, ACC, OFC, and right posterior superior TC. ◦Pre-Post PET changes were similar between Tx and PBO	Ordering Bias Post-Hoc No MCID Not Replicated
Nakal (2005)	Enrolled: 11	DBPCCT	Alosetron 2 weeks	◦No clinical pain measure reported ◦ Rectal Distention paradigm set at “level 3” pain.	α-{^{11}C]methyl-L-tryptophan PET during rectal distention before and after Tx: ◦Tx-related gender difference in PET uptake	Probe Power Ordering Bias Post-Hoc No MCID Not Replicated
Morgan (2004)	Enrolled:22 Complete: 19	DBPCCT	Amitriptyline 4 weeks	◦Pain VAS: change scores not provided; no difference between amitriptyline and PBO ($p=0.2$) ◦Rectal Distention VAS: Improvement 0.8 ($p=0.1$)	Rectal Distention BOLD measurements before and after Tx: ◦ Decreased BOLD with AMY in the ACC and left PPC. ◦No comparison between Tx and PBO	Post-Hoc No MCID Not Replicated
Lee (2012)	Enrolled IBS: 17 Enrolled controls: 17	SBPCT	Conditioned PBO	Pain VAS (0–100):	Rectal Distention BOLD measurements	Probe Not replicated

Author (Year)	n	Study Design	Treatment	Treatment Effect	Neuroimaging Technique and Findings	Design Problems
				◦IBS PBO Improvement 16.7 ($p<0.05$) ◦ Control PBO Improvement 20.6 ($p<0.05$)	No PBO compared to conditioned PBO: ◦Control and IBS have different BOLD patterns after PBO.	

*Data derived from Figures, not reported in text

†p-value repuria.1 “uncorrected” for multiple comparisons

‡The pre-treatment results reported here are also reported in Guedj (2007) Eur J Nucl Med Mol Imaging 34:1274–1279

▰Denotes study that used same cohort to report multiple results