Neuroimaging of Pain

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Richard H. Gracely and Pia C. Sundgren

Introduction

Pain is a private experience without objective physical correlates. In the past decades there have been tremendous advances in the understanding and treatment of pain. Yet the underlying mechanisms of many pain conditions are not known and many conditions have no effective treatment. The advent of modern dynamic neuroimaging has provided tools to reveal supraspinal pain processing and to help unravel the mysteries of many intractable pain syndromes. These tools have increased the understanding of altered central nervous system (CNS) processing in different chronic pain conditions and the underlying mechanisms mediating treatment response to pharmacological or other therapeutic interventions such as acupuncture or nerve stimulation. These techniques include conventional magnetic resonance imaging (MRI) and additional MR techniques such as functional MRI (fMRI), MR spectroscopy, and diffusion weighted and diffusion tensor imaging. Evidence from these MR methods and other techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) have further increased our knowledge about these conditions, their underlying etiology, and changed our way of thinking. Pain pathology can be associated with altered brain processing that is assessable to structural and functional neuroimaging.

This chapter has been revised from the original published in 2010. Sections on the history of pain neuroimaging and extensive descriptions of neuroimaging methodologies have been shortened. The interested reader is referred to the previous version and to comprehensive descriptions of methods in the current volume. This revised chapter includes knowledge gained since 2010 and updates advances in functional neuroimaging methodology. The choice of fibromyalgia (FM) as a candidate pain condition has been expanded to include similar conditions of irritable bowel syndrome (IBS), temporomandibular disorder (TMD), vulvodynia or vulvar vestibulitis syndrome (VVS), and chronic fatigue syndrome (CFS). We address the gap between the world of research neuroimaging and the demands of diagnosing and treating clinical pain conditions. We are particularly qualified for this discussion since individually we represent the separate sides of this gap; pain research (RHG) and clinical radiology (PCS). We consider the issues for clinical utility, especially the challenge of single person functional neuroimaging. We further consider the issues specific to the evaluation of human pain, including establishing the presence of pain, pain disability, pain diagnosis, pain treatment selection, and evaluation of pain treatment efficacy. Many of these issues are similar to parallel attempts to use functional neuroimaging for other purposes such as lie detection. We conclude with a review of recent results in conditions such as low back pain (LBP) and a systematic review of the results in FM, IBS, TMD, VVS, and CFS.

The clinical utility of the functional neuroimaging of pain is currently unknown. The major issues for such utility can be broadly divided into two parts; the general clinical utility of functional neuroimaging and the issues specific to pain evaluation and treatment.

Clinical Utility of Functional Neuroimaging

The important issues of applying functional neuroimaging to clinical decisions about an individual pain patient are similar to those for most any medical disorder. These have been cogently described in Chap. 25. Since most methods infer

R. H. Gracely
Center for Pain Research and Innovation, Department of Endodontics, School of Dentistry, School of Medicine, University of North Carolina, Chapel Hill, Chapel Hill, NC, USA
e-mail: richardgracely@unc.edu; Richard_Gracely@unc.edu

P. C. Sundgren (✉)
Department of Diagnostic Radiology, Clinical Sciences Lund, Lund University, Lund, Sweden

Department for Medical Imaging and Physiology, Skåne University Hospital, Lund, Sweden
e-mail: pia.sundgren@med.lu.se

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neural activity from regional cerebral blood flow (rCBF), results can be distorted by vascular pathologies. Distortion of fMRI BOLD images at tissue interfaces is increased by higher field strengths chosen to overcome problems with statistical power that afflict single subject analysis. Indwelling surgical clips can cause signal loss localized precisely at the area of interest. Head movement can hinder interpretation, especially when movement is synchronized with stimulation as in evoked pain studies. Many functional imaging paradigms rely on tasks. Task performance may be influenced by practice effects and by cognitive impairments. Limiting analysis to an individual limits the analytic power and also may result in poor normalization, and thus the ability to compare results to a normative sample.

Approaches to these problems are interrelated. Distortions can be minimized by choice of scan sequence or by use of alternative method such as arterial spin labeling (ASL) that are less susceptible to distortion. However, ASL is not as sensitive as the fMRI BOLD technique, and thus used at higher field strengths to increase sensitivity. The difficulty of tasks can be matched to patient ability, and task paradigms can be designed to control for practice effects. The lack of analysis power can be mitigated by alternative strategies such as conjunction analysis, which evaluates the overlap of results of multiple tasks; increased power is achieved by an individual performing multiple tasks, rather than by multiple individuals performing the same task.

Many of these issues such as distortion are associated with fMRI and, as with the case of ASL, can be mitigated by the use of alternative imaging approaches. In addition, clinical applicability depends on an interaction of imaging approach and the targets of this approach. Currently, the only accepted clinical application is presurgical mapping. In a modern alternative publication format (blog response to a tweet), Bandettini and Wong enumerate other pairs of approaches and targets that are more closely ready for clinical application (http://www.thebrainblog.org/2018/05/18/if-how-when-fmri-might-go-clinical/). The most promising is an evaluation of perfusion deficits by resting state BOLD that is currently being used in several hospitals. Analysis of the same deficits using the less sensitive method of ASL is also feasible, although requiring longer acquisition times to compensate for the lower sensitivity. Also promising is the combined approach of measuring perfusion with ASL and blood volume with BOLD or vascular space occupancy (VASO). This combined approach during normal or stress (breath hold or CO_2 inhalation) conditions can inform baseline blood oxygenation, neurovascular coupling, and changes in cerebral metabolic rate ($CMRO_2$).

In addition to these promising applications, functional localization of brain targets for stimulation by invasive deep brain stimulation, non-invasive transcutaneous magnetic stimulation (TMS), and transcutaneous direct current stimulation (tDCS) are close to the level of clinical utility. In all of these cases, functional measures are essentially providing structural information. Bandettini and Wong's blog also lists other candidates that form another tier of possible applications. These include biomarkers for disorders or diseases, modification of neural activity by biofeedback, assessment of "locked in" patients, localization of seizure foci, and general demonstration of the clinical importance of basic neuroscience.

The Specific Problem of Clinical Pain Assessment

The difficulties of translating neuroimaging results to clinical decisions are compounded further when the target is pain. There is general agreement that pain is a subjective experience that can only be assessed by verbal report. Many studies have sought an objective measure but none have provided sufficient sensitivity and specificity to replace a person's description of private experience [1]. This concept is described by a simple example. Imagine waking up in hospital in the middle of the night in severe pain. You press the call button and it is answered by a person who enters your room, looks at a meter, and informs you that, "sorry, I can't give you any pain medication because this device indicates that you really do not have any pain." This error of a false negative is one of many ethical and legal concerns about the development of an objective pain measure that are described below.

So how is pain evaluated? An important step is to define the target. Considerable evidence supports the concept that pain is both a sensory/perceptual event and a motivational state that influences behavior. The sensory aspects can be described by an intensity dimension and by a number of sensory qualities that specify mechanical perceptions (e.g., squeezing, pulling, traction, rotational, and punctate pressure), thermal qualities (e.g., hot, cold, freezing, burning), temporal qualities (e.g., constant, tingling, pounding), spatial qualities (e.g., spreading, shooting, deep, superficial), and unnatural qualities (e.g., electric shock). The motivational aspects focus on the disagreeable nature of pain with descriptions such as unpleasant and intolerable. This recognition has resulted in two fundamentally different approaches to pain measurement. One approach evaluates the two dimensions of sensory intensity and unpleasantness that are common to practically all pain experience [2, 3]. The other, complementary, approach evaluates these dimensions and also the variety of pain qualities that distinguish one type of pain from another [4–6].

These methods have been used in experimental studies that validate pain dimensions and provide checks of internal consistency [7, 8]. Clinically, these methods distinguish clin-

ical conditions and assess the efficacy of pain treatments. In the clinic these measures supplement clinical impression and evaluation of motor and social behavior and environmental factors that influence pain expression. For example, what are the factors in a patient's home life or job situation that reinforce pain behavior? Behavior is also dependent on the purpose of pain. There is growing appreciation of two types of pain. In the common conception of acute pain, the motivation is to avoid or minimize injury. Pain promotes immediate behavior of withdrawal that supplements natural motor reflexes. However, once injured, excitatory mechanisms use pain to inhibit movement to immobilize and protect the injured region to maximize healing. In the acute case pain evokes movement, in the potentially chronic case movement evokes pain [9, 10].

In addition to these varying "pain targets," there are multiple goals of pain assessment and different methods are more appropriate for specific goals. Goals that could potentially benefit from functional neuroimaging include (1) Establishing the Presence of Pain, (2) Differential Diagnosis, (3) Treatment Planning, and (4) Evaluation of Treatment. The first goal is the central issue in legal determinations of disability and also central to current concerns about opioid analgesic abuse. Several publications have addressed this goal and the most extensive treatment is from a recent publication by a task force of prominent pain scientists established by the International Association for the Study of Pain [11]. This extensive treatment established seven criteria for neuroimaging protocols: (1) precise definition of a pain neuromarker; (2) applicability of the pain neuromarker to individuals; (3) methodological procedures used during pain testing must be validated; (4) measures must be internally consistent, and the quality of imaging data validated for the individual tested, using positive and negative controls; (5) the neuromarker must be diagnostic for pain; (6) the neuromarker must be validated with converging methods; and (7) the neuromarker must be generalizable to the patient group tested and to the test conditions.

This consensus statement has set a necessary high bar for functional neuroimaging determination of the presence of chronic pain. The task force further concluded, "The admissibility of such evidence in legal cases also strongly depends on laws that vary between jurisdictions. For these reasons, the task force concludes that the use of brain imaging findings to support or dispute a claim of chronic pain—effectively as a pain lie detector—is not warranted, but that imaging should be used to further our understanding of the mechanisms underlying pain."

Thus, an objective measure of the presence of pain must satisfy both the general issues of applying research methods to clinical decision making described above and the issues specific to the fact that to date pain has no verified objective correlate. Interestingly, although the likelihood of the demonstration of a pain biomarker by neuroimaging is presently remote, functional neuroimaging may be the most likely method of determining pain presence. The combination of multiple methods applied over the whole brain may yield patterns that uniquely indicate pain or at the least are necessary for the demonstration of either the presence or absence of pain. Said another way, neuroimaging may reduce both the errors of false positive and false negative to indicate pain, or perhaps attenuate one of these errors.

Once the presence of pain is established, functional neuroimaging is likely to aid clinical diagnosis and, once diagnosis is made, these methods have the potential to guide choice of treatment and evaluation of treatment success. Current studies have evaluated effects ranging from potent pharmacological interventions with opioid analgesics to non-pharmacological interventions such as cognitive behavioral therapy (CBT), mindfulness meditation, hypnosis, and acupuncture. Related are the influence of variables such as mood, negative affect, attachment, resilience, and empathy**.**

Classifications of Neuroimaging

The range of neuroimaging methods can be classified by a number of dimensions such as use of radioactive injectable tracers, use of any tracer, spatial and temporal resolution, measurement of structure or function, dependence on regional cerebral blood flow (rCBF) as an indicator of neural activity, scan duration, applicability to an individual versus a group of individuals, imaging distortions, confounds with movement, and reliability. One important dichotomy is the need for an intervention. Methods such as BOLD fMRI usually measure change in response to some external event while other "static" methods can measure steady states and assess differences between individuals. Some static measures can also measure changes before and after an intervention. Both types of measures are used to assess pain, for example, examining static measures between persons with chronic pain and control subjects versus measuring the brain response to a brief painful stimulus. There is considerable evidence from studies using both painful and non-painful stimulation.

Since the initial positron emission tomography (PET) studies in 1991 [12, 13], a growing literature has evaluated brain activity evoked by the application of painful stimuli. PET imaging demonstrated patterns of brain activation in response to stimulation by either brief or prolonged heat and cold and by injection of ethanol or capsaicin [14–19]. These studies coincided with the maturation of functional MRI (fMRI) methods that used BOLD methods to reveal patterns of brain regions activated by commonly used mechanical, heat, cold, electrical stimuli, and unique stimuli such as electrical muscle stimulation and painful hallucinations [20–22].

The activated regions were interpreted as a network termed the "pain matrix" [23]. This description implied a functional organization evaluated by appropriate methods such as structural equation modeling [24] and by additional imaging methods with increased temporal resolution such as magnetoencephalography (MEG) [25, 26]. The initial studies showed that painful stimulation commonly activates thalamus, and primary and secondary somatosensory cortex, cerebellum, anterior insular and cingulate cortices, basal ganglia, and both frontal regions and posterior parietal cortex. Subsequent studies have further refined pain network concepts to the extent that "pain matrix" is no longer a useful term, since many of the components are not specific to pain.

These studies have also contributed to increased understanding of somatotopic representation of body regions. Correlation of the location of stimulus and evoked activity has demonstrated somatotopic organizations within somatosensory cortices, insular cortex, anterior cingulate cortex, supplementary motor area, and putamen [27]. Pertinent to the theme of this volume, some of these procedures have been standardized for possible clinical applications. For example, Stippich et al. have developed a fully automated tactile stimulation system to provide somatotopic maps of primary [28] and secondary [29] somatosensory cortex within 1–2 min.

These initial "stimulate and see what you get" designs have both confirmed and contributed to the knowledge base of functional neuroanatomy in terms of the regions activated by pain, the presence of somatotopic maps, and the functional interconnections among these regions. More elaborate designs have assessed the influence of a large number of antecedent variables and the influence of specific interventions on both static activity and on the interaction with evoked activity.

Several studies have explored a number of factors directly related to painful stimulation. These designs have explored antecedent effects such as anticipation, influence of expectancies, predictability, and directed attention [30–37]. Anticipation of pain has been shown to activate regions within the medial frontal lobe, insular cortex, and cerebellum close to those activated by pain [38]. Similar activations evoked by anticipation and placebo analgesia suggest a common mediating network that includes dorsolateral prefrontal cortex (DLPFC), medial frontal cortex, and the anterior mid-cingulate cortex [39]. These effects are pertinent to both the special case of procedural pain in which a patient expects a painful event, and to analgesic conditions in which pain relief is expected. These results may also be relevant to the many cases of movement-evoked pain experienced in arthritic conditions, low back pain, or complex regional pain syndromes. They are likely less relevant to persistent spontaneous pain associated with many chronic pain syndromes.

Antecedent factors vary along a continuum of current "state" variables to more persistent or fixed "trait" variables. In addition to anticipation, imaging studies have evaluated the effects of state variables such as comorbidities or negative mood [40, 41], and of trait variables such as early life experiences [42, 43], personality characteristics such as resilience [44–46], and the effects of gender [45, 47–51]. Midway along this continuum is persistent but variable states such as the influence of attachment figures [52]. Other within-individual changes are evaluated by inducing cytokine expression [53] or contrasting responses during the clinical state to those after the resolution of the condition [54].

An interesting and extensive series of studies has investigated the effects of empathy toward pain in other individuals [55]. In these studies, subjects imagine other people in pain or actually observe these persons. Empathy appears to activate regions in anterior insular, anterior mid-cingulate, and posterior parietal cortices, and to be modulated by factors such as attention, reality, social context, and perceived agency or fairness in others [56–58]. The activated regions appear to be related to the affective as opposed to sensory pain processing [58]. An intriguing study evaluated empathy for pain in individuals who have never experienced pain due to congenital pain insensitivity. Using fMRI, these individuals showed normal responses in anterior insula and anterior mid-cingulate cortex to observed pain, suggesting that responses observed in these regions may be related to emotional rather than pain processing [59].

Since both the mechanisms of pain and the mechanisms of many pain treatment procedures are not completely known, a large number of neuroimaging studies have examined the effects of pharmacological or nonpharmacological analgesic treatments on pain responses. Pharmacological interventions include the acute administration of the opioids fentanyl, alfentanil, remifentanil, and morphine, the opioid antagonist naloxone, the anesthetics ketamine and propofol, and a number of specific receptor agonists and antagonists [60–68]. These studies have distinguished between the mechanisms of pain relief provided by an active analgesic or placebo medication, and demonstrated differential effects on two main dimensions of subjective pain experience. As noted above, pain can be described by both the intensity of the evoked sensation and the unpleasantness of these sensations [7]. Oertel et al. [69] found that pain-evoked activity assessed by fMRI in brain regions implicated in sensory processing, such as primary and secondary somatosensory cortex and posterior insula, was attenuated in a dose-dependent manner by alfentanil. In contrast, brain regions implicated in the processing of pain unpleasantness (e.g., anterior insula, amygdala, cingulate cortex) were inhibited at even the lowest dose.

Pain is also treated successfully without drugs. A broad range of methods can be roughly divided into those that involve or do not involve a physical intervention. Physical interventions range from simple massage and physical therapy to stimulation of the brain through implanted electrodes. Perhaps because of ease of administration and regulatory

simplicity, the effects of acupuncture have been extensively studied with neuroimaging, with studies of repeat reliability, short- and long-term effects, use of non-penetrating placebo needles, point specificity, manual versus electroacupuncture, and low versus high frequency electroacupuncture [36, 70–74]. Accumulating evidence suggests activation of limbic and neocortical systems and interruption of default mode processing during the resting state. Other studies have evaluated the effects of spinal cord stimulation, and electrical or magnetic cortical stimulation (rTMS) [75–77].

In contrast to these physical interventions, neuroimaging has assessed the cerebral effects of pain control by non-physical methods such as hypnosis or meditation [78, 79]. In a series of studies, Zeiden has explored the neural mechanisms or pain reduction via the meditative practice of mindfulness. While mindfulness is usually trained, Zeiden and colleagues also observed that mindfulness as a trait characteristic was associated with lower pain sensitivity at threshold levels, lower pain catastrophizing and less connectivity within the default mode network (DFN) [79]. This study also found increased connectivity between the DFN and somatosensory cortices, suggesting that the neuroimaging findings in high-trait individuals are consistent with the mindfulness training goals of increased focus on sensation and less focus on emotional appraisal. Zeidan's group has also demonstrated the presence of multiple mechanisms of pain reduction, providing evidence that the mechanisms of mindfulness pain reduction are neither mediated by endogenous opioids nor the analgesic mechanisms of sham mindfulness or administration of a placebo analgesic [80].

Pain reduction by an inert placebo is a fascinating topic in its own right and has been the focus of a large number of neuroimaging studies. While both actual and placebo treatments have been shown to reduce pain, these effects appear to be mediated by different mechanisms [32, 65, 81]. A comparison of results from Parkinson's Disease, pain, and depression suggest a common factor of modulation of cerebral "top-down" mechanisms [82]. Multiple mechanisms may be involved in placebo analgesia, including antecedent conditions of expectation, actual pain modulation, and modification of pain response [35]. The multiple placebo mechanisms can be distinguished from active treatment, and a number of studies have found imaging markers to actually predict placebo response [30, 31, 83–86].

Applying Neroimaging to Clinical Conditions

Many of the previously mentioned designs have been applied to individuals with specific pain syndromes, usually comparing the effects to those from healthy control populations. Visceral disorders have been studied extensively. These methods have been applied to visceral chest pain including heartburn (gastroesophageal reflux disease [GERD]) [87], although the majority have evaluated functional gastrointestinal (GI) disorders by using PET and fMRI to assess the effects of rectal balloon distension in patients with irritable bowel syndrome (IBS) and control subjects. These studies have identified mechanisms of central sensitization, activation of pain inhibitory mechanisms, and cortical interactions using structural equation modeling [24, 88–90]. The results provide basic evidence for mechanisms mediating visceral and cutaneous pain sensations, and increasing evidence for the pathophysiology of functional GI disorders that may guide development of more effective treatments.

A similar body of neuroimaging studies has investigated the neural basis of headache (HA). Studies of migraine and cluster headaches have identified both functional and structural changes [91, 92] that have advanced the understanding of headache mechanisms that could potentially aid in diagnosis and choice of treatment [93, 94].

The list of pain disorders evaluated by neuroimaging is vast and varied, including evaluation of neurosurgical patients, stroke patients, multiple sclerosis, epilepsy, chronic regional pain syndromes (CRPS), whiplash, spinal cord injury, burning mouth syndromes, trigeminal neuralgia, low back pain, tinnitus, photophobia, and hysterical anesthesia. A consistent literature has delineated marked cortical reorganization after amputation and brain activity related to phantom limb pain. In addition to the extensive literature on functional GI disorders, neuroimaging methods have been successfully applied to often comorbid conditions of temporomandibular disorder, chronic fatigue syndrome, vulvodynia, and fibromyalgia. All five conditions have been grouped together because of symptom overlap and largely unknown mediating mechanisms. They have been referred to as functional disorders, central sensitivity syndromes, and can be described by the International Classification of Diseases (ICD-11) as "Chronic Primary Pain" (CPP) conditions. There are distinct differences between these CPP syndromes, for example, the regional focus of temporomandibular disorder (TMD), irritable bowel syndrome (IBS), and vulvodynia syndrome (VVS) contrasts with the vague and generalized symptoms of fibromyalgia (FM) and chronic fatigue syndrome (CFS). An extensive review in 2016 discussed the neuroimaging results for these five disorders, discussing both the scientific merits and the clinical utility for each combination of disorder and neuroimaging method [95]. The following provides updates to this review and reiterates the possible clinical utility of specific neuroimaging methods. We first focus on MR spectroscopy and diffusion methods because these methods are already used clinically.

Molecular Measurement by MR Spectroscopy

MR spectroscopy (MRS) is a non-invasive MRI technique that quantifies the biochemical metabolites in brain or other tissue. MRS is currently used both in clinical practice and as a research tool in different pain conditions. Most commonly used is ^{1}H (proton) MRS due to high natural abundance of protons, high absolute sensitivity to magnetic manipulation, better spatial resolution, and relative simplicity of technique. Commonly evaluated CNS metabolites that can be related to pain are: *N*-acetylaspartate (NAA), choline (Cho), Creatine/phosphocreatine (Cr), myo-inositol (Ins), summed glutamate (glu) and glutamine (gln) (glx), and gamma-aminobutyric acid (GABA). The difficulty of measuring concentrations of some of these metabolites like glutamate and glutamine and GABA, potentially important metabolites in pain conditions, can be resolved by using ^{1}H-MRS at high magnetic field strengths (i.e., at least 3 T or more) due to the increased separation of metabolites with coupled resonances [96, 97]. Other metabolites such as NAA, Cho, Cr can be quantified adequately at lower field strength. Most commonly in investigation of different pain conditions, spectra are acquired using single voxel spectroscopy (SVS) with a spatial resolution in the order of 1–8 cm^3. This technique is time-efficient and acquires quantitative data. Figures 17.1 and 17.2 illustrate SVS voxel placements and a metabolic spectrum post-processed in LC-model (Figs. 17.1a–c and 17.2a–c).

The proper selection of appropriate MRS technique, including magnetic field-strength and measurement parameters such as echo time (TE) and repetition time (TR), is crucial. Investigations of different pain conditions require short echo times (TE = 20–35 ms) because of the need for detection of metabolites with short relaxation times, such as glutamate, glutamine, myo-inositol, glycine, GABA, and some amino-acids. *N*-acetylaspartate (NAA) serves as a measure of normal healthy neuronal tissue. Choline (Cho) has been implicated as a marker of cellularity and cell turnover. Creatine/phosphocreatine (Cr) is present in glial tissue and neurons and is involved in phosphate transport. Cr is a relatively stable metabolite used by most investigators as an internal control for quantifying other metabolites (i.e., metabolite ratios often include Cr as the denominator). Myo-inositol (Ins) is found in glial tissue and is thought to be involved as a second or third messenger for neurotransmitters. Glutamate (glu) is a major excitatory neurotransmitter that has been implicated as an important mediator in the neurotransmission and negative affect associated with pain. Glu is taken up by the astroglial cells, transformed into glutamine (Gln), and then transported back to the neuron to be recycled. GABA is the chief inhibitory neurotransmitter in the CNS system and can only be reliable quantified using magnetic high-field strength (>3 T). For future description of the MRS techniques and post-processing methods please refer to Chaps. 9 and 10.

Neuroimaging Studies of Pain Utilizing MR Spectroscopy (MRS)

Chronic Low Back Pain

In contrast to numerous articles utilizing fMRI and PET to study pain, the numbers of studies using MRS are limited (Table 17.1). However, in recent years there have been some reports utilizing in vivo single voxel proton magnetic resonance spectroscopy (^{1}H-MRS) to examine brain chemistry changes in patients with different chronic pain conditions. The majority of these earlier studies have been performed on a 1.5 T MR scanner while studies that are more recent are performed on a 3 T MR scanner. Most of these studies have focused on regions in the brain previously suggested by studies from fMRI and PET to be involved in pain processing. MRS has been performed in different conditions like chronic low back pain [98–101], complex regional pain syndrome type 1 [102], chronic neuropathic pain [103], temporomandibular disorder (TMD) [104, 105], and fibromyalgia [106, 107].

Reduction in *N*-acetyl aspartate (NAA) and glucose was detected in the left dorsolateral prefrontal cortex in a study of low back pain by Grachev et al. in 2000 [98] suggestive of neuronal loss and degeneration. This study evaluated several brain regions in the left hemisphere, most importantly prefrontal cortex, anterior cingulate cortex and thalamus, all considered to be involved in the "pain matrix" [23]. The interrelationship between chemicals within and across brain regions was abnormal, and there was a specific relationship between regional chemicals and perceptual measures of pain and anxiety. The duration of pain related to the chemical changes in cingulate cortex and the sensory and affective aspects of pain related to the concentrations of prefrontal metabolites. In a subsequent study from the same group, ten patients with low back pain (LBP) and depression and ten normal healthy subjects without depression (NC) were evaluated by single-voxel ^{1}H-MRS in right and left DLPFC anterior cingulate cortex (ACC), thalamus and orbital frontal cortex (OFC). Reduced NAA was found in the right DLPFC in patients with LBP and depression compared to NC ($p > 0.02$) [99]. The depression levels in LBP patients were highly correlated with the NAA levels in the right DLPFC ($r = -0.09$, $p < 0.0001$). In addition, the pain levels in chronic back pain (CBP) patients were also associated with the right DLPFC ($r = -0.62$, $p < 0.05$). Prefrontal NAA was more strongly associated to depression than to pain in CBP, suggesting that MRS mapping of NAA to the depression and pain measures might be used for segregation of their circuitries in the chronic pain brain. Another study performing single-voxel ^{1}H-MRS, with separate voxel placements in the same regions (i.e., prefrontal cortex, anterior cingulate cortex, and thalamus) demonstrated that it was possible to discriminate patients with low back pain from controls with a

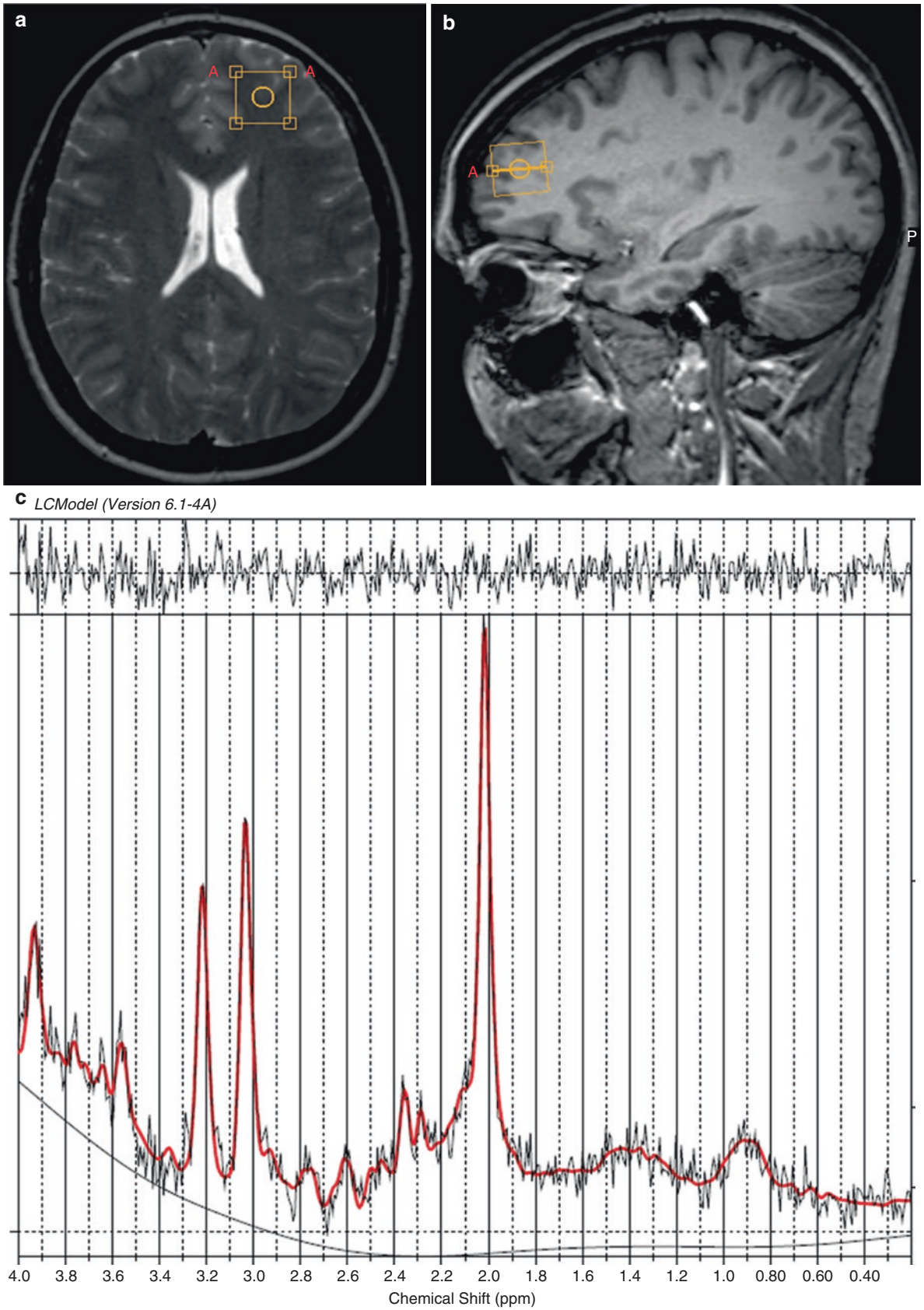

Fig. 17.1 Single-voxel ^{1}H-MRS (TE 30 ms, TR 3000 ms) performed in the left dorsal lateral prefrontal cortex (DLPFC) a region often involved in different pain conditions. Volume of interest (VOI) placed on axial T2-weighted (**a**) and sagittal T1-weighted (**b**) images of the brain. The spectra obtain from (**c**) the VOI presented using an automatic fitting program, the LC model

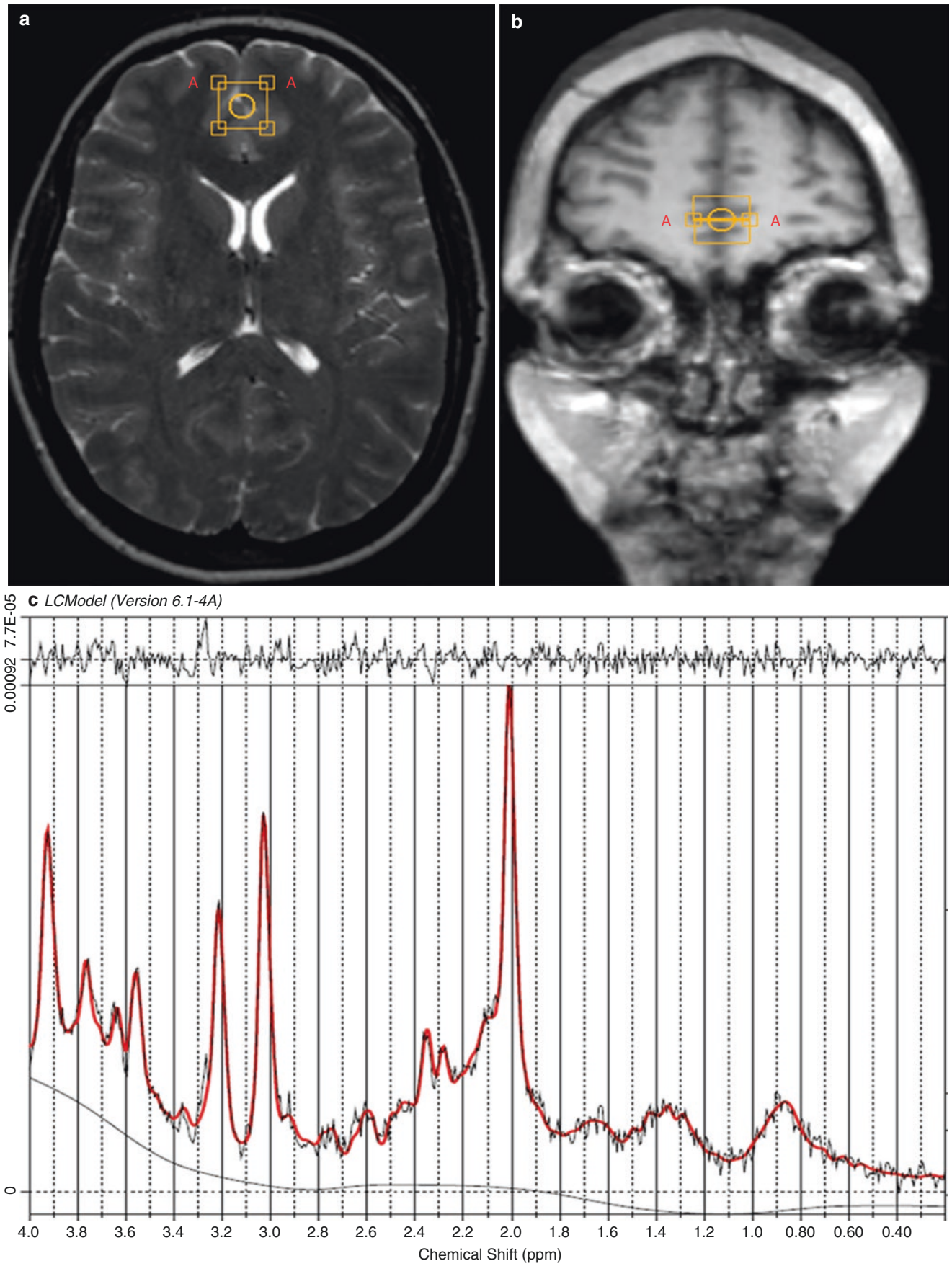

Fig. 17.2 Single-voxel ^{1}H-MRS (TE 30 ms, TR 3000 ms) performed in the anterior cingulate cortex (ACC) another of the regions involved in different pain conditions. Volume of interest (VOI) placed on axial T2-weighted (**a**) and coronal T1-weighted (**b**) images of the brain. The spectra obtain from the VOI (**c**) is presented using an automatic fitting program, the LC model

Table 17.1 Summary of MRS research in back pain and pain stimulation

Authors	Subjects	MRS method	Summarized findings
Grachev ID, et al., 2000	9 CLBP patients and 11 HC	SVS ^{1}H-MRS, STEAM, TE 30 ms, TR 1500 ms performed in nine different brain regions	Reduced NAA and glucose in DLPFC with correlation to pain and anxiety
Grachev ID, et al., 2003	10 CBP with depression, 10 HC	SVS ^{1}H-MRS, STEAM, TE 30 ms, TR 1500 ms, performed in different brain regions	Reduction in NAA in right DLPFC in LBP patients, depression levels negatively correlated to NAA levels in DLPFC. NAA levels negative correlated to pain but weaker then depression
Mullins, et al., 2005	12 HC	4 T, SVS ^{1}H-MRS, STEAM, TE 20 ms, TR 2000 ms 2 scan prior and during cold pressor stimulation, pain rating scale 0–10	Significant increase of Glu and trend towards increase of gln and significant increase of glx during pain stimulation in anterior cingulated cortex
Siddall PJ, et al., 2006	32 patients with LBP and 33 HC	SVS ^{1}H-MRS, STEAM. TE 25 ms, TR 1500 ms Try to differentiate LPB from HC by changes in spectral pattern	Differentiation between patients with LBP versus HC with 100%, 99%, and 97% accuracy based in findings in ACC, thalamus, PFC
Kupers R, et al., 2009	13 HC	3 T, SVS ^{1}H-MRS, double spine echo method, TE 20 ms, TR 3000 ms	Significant increase in GABA concentration in rACC during and after tonic heat stimulation

HC healthy controls, *LBP* low back pain, *CBP* chronic back pain, *TE* echo time, *TR* repetition time, *STEAM* stimulated-echo acquisition mode pulse sequence, *Glu* glutamate, *Gln* glutamine, *Glx* sum of glu+gln, *NAA* *N*-Acetylaspartate, *Cho* choline, *Cr* creatine, *DLPFC* dorsolateral prefrontal cortex, *PFC* prefrontal cortex, *ACC* anterior cingulate cortex

respective accuracy of 100%, 99%, and 97% for the different areas [100]. This study used a particular pattern recognition method developed specifically for biomedical spectroscopy data, the "statistical classification strategy" (SCS). Another recent study demonstrated decrease of Glu in the anterior cingulate cortex (ACC) as well as reduced myo-inositol in ACC and thalamus [108]. In contradiction, no significant changes of Glu/GABA ratios, or Glx were shown in the ACC, insula, posterior cortex, or SCC [109].

Overall several MRS studies have provided evidence that patients with CLBP have alterations in the biochemical metabolic profile, suggesting that biochemical changes may play a significant role in the development and pathophysiology of CLBP.

Complex Regional Pain Syndrome Type I (CRPS Type I)

Decreased levels of NAA have also been demonstrated in the dorsolateral prefrontal cortex in patients with complex regional pain syndrome type 1 (CRPS type 1) [102]. These studies suggest that NAA might be a marker for chronic pain indicating neuronal degeneration.

Neuropathic Pain

MRS has also been utilized to evaluate patients with neuropathic pain. Seven patients with chronic neuropathic pain after spinal cord injury (SCI) were compared to nine patients with SCI but without pain and ten healthy controls [110]. Single-voxel ^{1}H-MRS was performed in the region of thalami bilaterally. NAA was negatively correlated with pain intensity (r = –0.678) and myo-inositol (Ins) was positively correlated with the average pain intensity (r = 0.520). The authors suggested that the decrease in the NAA concentrations in SCI patients could represent a dysfunction of inhibitory neurons due to deafferentation resulting in greater activity of excitatory neurons and a heightened sensation of pain. A small recent pilot study demonstrated reduction in pain, and an increase in both Glx/Cr and NAA/Cr in the ACC after treatment with transcranial current stimulation (tDCS). The authors pointed out that the observed increase in NAA/Cr is consistent with the possibility that tDCS improves the descending pain modulation system by increasing the neuronal activity in the ACC [111].

Chronic Fatigue Syndrome (CFS)

The pathogenic mechanisms that mediate chronic fatigue syndrome (CFS) are not fully understood. A study of eight patients with CFS and eight normal controls reported significantly higher Cho/Cr ratios (0.76; p = 0.008) in the occipital cortex in adult patients [112] and another study reported increased Cho/Cr ratio in the basal ganglia in a group of pediatric patients aged 11–13 years [113]. Significantly, elevated Cho has also been demonstrated in the basal ganglia in a group of adult CFS patients compared to normal controls [114]. No morphological brain abnormalities were observed on conventional MRIs in any of the published cases. The underlying mechanism for the elevated choline in CFS is still unknown. Possibilities include higher cell membrane turnover due to gliosis or altered intramembrane signaling, or an abnormality of the phospholipid metabolism [112, 114, 115]. Hippocampus has also been targeted in patients with CFS. An MRS study of 7 CFS patients and a control cohort of 10

healthy individuals utilizing single-voxel ^{1}H-MRS demonstrated a significant decrease of NAA concentration in normal-sized right hippocampus in the CFS patients compared to healthy controls (10.8 ± 0.6 versus 14.1 ± 0.7) (p = 0.005) [116]. These findings suggest reduced neural/glial metabolism that may be normalized by treatment with a long-acting β-1/β-2 (beta-1/beta-2) receptor antagonist as described in a patient with fibromyalgia who had abnormal NAA/Cr ratios in right hippocampus [117].

In contrast to these specific single voxel targets, a recent study performed MRS at 47 regions throughout the brain in 15 CFS patients and 15 control subjects. The analysis showed increased CHO/CR in left anterior cingulate and found associations with fatigue in seven regions. The authors also used MRS to assess brain temperature and found elevations in right insula, putamen, frontal cortex, thalamus, and cerebellum, suggesting neuroinflammation [118].

Temporomandibular Disorders and Orofacial Pain

Temporomandibular disorders (TMD) include craniocervical pain conditions with unclear etiologies. There are few MRS studies of TMD patients. In a SVS (1)H-MRS study of the right and left posterior insular (11 individuals with myofascial TMD and 11 matched control individuals) metabolites were assessed before and after pressure-pain of both the right anterior temporalis muscle and the right thumbnail. Glu levels were significantly lower in all individuals after pain testing. In patients with TMD the left-insular Gln levels were related to reported pain. The NAA and Cho levels in the left posterior insula were significantly higher at baseline in TMD patients than in control individuals, and the NAA levels significantly correlated with pain-symptom duration [104]. Another study demonstrated significantly higher Cr levels within the posterior insula in patients with regional TMD or general TMD pain than in healthy controls. Cho concentration correlated negatively to maximum mouth opening capacity with or without pain as well as to pressure-pain threshold on the hand, and the concentration of Glu correlated positively to temporal summation to painful mechanical stimuli [105].

Overall, these findings provide new evidence about the critical involvement of the posterior insular cortex and the neurobiology underlying TMD pain in both regional and generalized manifestations. These results may potentially contribute to the diagnosis and management of TMD patients.

Fibromyalgia (FM)

Fibromyalgia is a chronic pain condition characterized by widespread pain. The former American College of Rheumatology (ACR) diagnostic criteria require the presence of pain in all four quadrants of the body and in the axial skeleton and tenderness as demonstrated by pain to 4 kg of manual pressure in at least 11 of 18 predefined "tender point" locations. These diagnostic criteria have been modified to deemphasize demonstrated tenderness [119]. Fibromyalgia is rarely observed alone and is often comorbid with other CPP syndromes in this group. Sensitivity to stimulation is not confined to pressure, but includes sensitivity to painful thermal and electrical stimulation [120].

FM has been associated with changes in hippocampal brain metabolite ratios, especially a significant decrease in NAA/Cr ratio in the right hippocampus [117, 121]. A single voxel ^{1}H-MRS study in 16 female FM patients and 8 healthy controls demonstrated significant reduction in the NAA/Cr ratio in the right hippocampus and a significant negative correlation between patients score on the Fibromyalgia Impact Questionnaire and NAA/Cr ratio in the right hippocampus. Similar findings were presented in a case report from the same research group. In that case report the patient's abnormal NAA/Cr ratios normalized and an improvement of her clinical symptoms occurred after medical treatment [117]. In 2008, Emad et al. also utilized a single-voxel ^{1}H-MRS to evaluate metabolic changes in the hippocampus in patients with FM and reported significant reduction of NAA concentration and decreased NAA/Cr ratio in bilateral hippocampi and elevated Cho concentrations in the left hippocampus [122]. This study found significant positive correlation between the levels of Cho and Cr in the right hippocampus and the language score of the Mini Mental State Examination (MMSE) used to assess cognitive function.

Other investigators have used MRS to investigate the potential for brain metabolite changes in FM. In 2008, Harris et al. demonstrated changes in the glutamate Glu/Cr ratios within the insular cortex, an area implicated in augmented pain perception in FM, in response to treatment in a study using single-voxel ^{1}H-MRS [123]. Pre- and post-treatment Glu/Cr ratios were negatively correlated with changes in experimental pain thresholds and positively correlated with changes in clinical pain. In another study from the same research group, participants underwent pressure pain testing and single-voxel ^{1}H-MRS in the right anterior insula and right posterior insula. In comparison to 14 age- and sex-matched pain-free controls, 19 FM patients had significantly higher levels of Glu (mean ± SD 8.09 ± 0.72 arbitrary institutional units versus 6.86 ± 1.29 arbitrary institutional units; p = 0.009) and combined glutamine (Gln) and Glu (i.e., Glx) (mean ± SD 12.38 ± 0.94 arbitrary institutional units versus 10.59 ± 1.48 arbitrary institutional units; p = 0.001) within the right posterior insula. Moreover, they reported that in the right posterior insula higher levels of Glu and Glx were associated with lower pressure pain thresholds across both groups for medium pain (for Glu, $r = -0.43$, p = 0.012; for Glx, $r = -0.50$, p = 0.003). Both studies concluded that enhanced glutamatergic neurotransmission resulting from higher

concentrations of Glu within the posterior insula may play a role in the pathophysiology of FM and other central pain augmentation syndrome. Petrou et al. from the same research group demonstrated, using a different method of spectroscopic analysis—2D-CSI MRS, Cho/Cr variability in the right dorsolateral prefrontal cortex (DLPFC) when comparing FM patients and healthy controls [107]. This variability in Cho/Cr levels within the patient group appeared to be a "widespread" phenomenon, because those with low levels in one brain region typically had low levels in the other, and vice versa, whereas no such association was found within controls. They also reported a significant correlation between the Cho/Cr ratios and clinical pain in DLPFC (dorsolateral prefrontal cortex) in FM patients and evoked pain threshold correlated significantly with NAA/Cho ratios in the left insula and left basal ganglia [107]. Significantly elevated Glx/Cr and Glu/Cr ratios have also be demonstrated in FM patients compared to healthy controls within the right and left VLPFC (ventrolateral prefrontal cortex) [124].

There are indications that transcranial direct current stimulation (tDCS) improves pain symptoms in fibromyalgia (FM). In a recent study 12 FM patients underwent sham tDCS over the left motor (anode) and contralateral supraorbital cortices (cathode) (M1-SO) for 5 consecutive days, a 7-day washout, followed by active M1-SO tDCS for 5 consecutive days. The authors found significant decrease in clinical pain scores between baseline and active tDCS time-points ($p = 0.04$) as well as significant decrease in Glx in the anterior cingulate ($p = 0.013$) for the sham-active tDCS comparison. For the baseline-sham tDCS comparison, there was a significant increase in *N*-acetylaspartate (NAA) levels in the posterior insula ($p = 0.015$). A trend toward increased γ-aminobutyric acid (GABA) in the anterior insula for the baseline-active tDCS comparison ($p = 0.064$) and a decrease in Glx in thalami for the sham-active tDCS comparison [125].

MRS has also been used to evaluate medical treatment with memantine in 25 FM patients. Patients treated with memantine demonstrated significant increase in the glutamate ($p = 0.010$), glutamate/creatine ratio ($p = 0.013$), combined glutamate + glutamine ($p = 0.016$) and total *N*-acetyl-aspartate (NAA+NAAG) ($p = 0.034$) in the posterior cingulate cortex compared with those on placebo. In addition, this study found significant increase in Cr and Cho in the right posterior insula and a correlation between Cho and scores on the Fibromyalgia Impact Questionnaire [126].

See Table 17.2 for a summary of key articles on MRS research of fibromyalgia.

Table 17.2 Summary of MRS research in fibromyalgia

Authors	Subjects	MRS method	Summarized findings
Harris RE, et al., 2008	10 FM	SVS ^{1}H-MRS, PRESS, TE 30 ms, TR 3000 ms SVS ^{1}H-MRS, PRESS, TE 30 ms, TR 3000 ms experimental pain stimulation and clinical pain testing and questionnaire. Treated with 4 weeks of acupuncture or sham acupuncture	Experimental pain and clinical pain reduced in FM patients after 4 weeks of acupuncture. Changes from pre- to post-treatment in Glu/Cr were negatively correlated with changes in experimental pain thresholds and positively correlated with changes in clinical pain
Petrou M, et al., 2008	21 FM and 27 HC	2D-CSI ^{1}H-MRS, PRESS, TE144 ms TR 1500 ms, VOI level of bgl and above ventricles	Greater variations in Cho/Cr ratios I DLPFC in FM vs. HC, positive correlation between Cho/Cr ratios in DLPFC and pain in FM. Positive correlation NAA/Cho in left Bgl left Insula
Wood PB, et al., 2009	16 female FM 8 HC	SVS ^{1}H-MRS, PRESS TE 35 ms, TR 1500 ms	Significant reduction in NAA/Cr and negative correlation with FIQ scores and NAA/Cr ratio in right hippocampus
Harris RE, et al., 2009	19 FM, 14 HC	SVS ^{1}H-MRS, PRESS, TE 30 ms, TR 3000 ms Experimental pain stimulation and clinical pain testing and questionnaire	Significantly higher levels of Glu and combined glutamine and Glu (i.e., Glx) within the right posterior insula in FM. The right posterior insula higher levels of Glu and Glx were associated with lower pressure pain thresholds

FM fibromyalgia, *HC* healthy controls, *TE* echo time, *TR* repetition time, *PRESS* point resolved-echo stimulated spectroscopy, *FIQ* Fibromyalgia Impact Questionnaire, *DLPFC* dorsolateral prefrontal cortex, *Bgl* basal ganglia, *glu* glutamate, *gln* glutamine, *glx* sum of glu+gln, *NAA N*-Acetylaspartate, *Cho* choline, *Cr* creatine

Temporomandibular Disorder (TMD)

TMD includes craniocervical pain conditions with unclear etiologies. Few MRS studies have been performed in TMD patients. In a SVS (1)H-MRS study of the right and left posterior insular (11 individuals with myofascial TMD and 11 matched control individuals) metabolites were assessed before and after pressure-pain of. Glu levels were significantly lower in all individuals after pain testing. In the patients with TMD the left-insular Gln levels were associated with reported pain. The NAA and Cho levels in the left posterior insula were significantly higher at baseline in TMD patients than in control individuals, and the NAA levels significantly correlated with pain-symptom duration [104]. Another study demonstrated significantly higher tCr levels within the posterior insula in patients with regional TMD or general TMD pain than in healthy controls. Cho concentration correlated negatively to maximum mouth opening capacity with or without pain as well as pressure-pain threshold on the hand, and the concentration of Glu correlated positively to temporal summation to painful mechanical stimuli [105].

Overall, these findings provide new evidence about the critical involvement of the posterior insular cortex and the neurobiology underlying TMD pain in both regional and generalized manifestations, with possible indirect implications for the diagnosis and management of TMD patients.

Irritable Bowel Syndrome (IBS)

A study of 15 IBS patients and 15 controls found targeted bilateral hippocampi and found a reduction of glutamate-glutamine (Glx) in the IBS patients. Glx levels were inversely related to emotional stress in the patients but not in the control subjects [127].

Vulvodynia (VVS)

No studies have been performed although several investigators have used MR spectroscopy in studies of pelvic pain in women [128–130].

Evoked Pain in Healthy Control Subjects

The brain's response to painful stimuli has been investigated in MRS studies of the anterior cingulate cortex [131, 132]. Several fMRI and PET studies have demonstrated involvement of the anterior cingulate cortex in the affective processing of pain [20, 21, 133–136]. Similar findings have been found in a few MRS studies. Mullins et al., in a single-voxel ^{1}H-MRS study, found increased glutamate and glutamine concentrations compared to baseline in the anterior cingulate cortex during painful stimulation. The glutamate increased 9.3% from baseline and the increase in glutamine levels correlated strongly with subjective level of pain experienced by the subjects ($r^2 = 0.58$, $p < 0.01$) [132]. In a study of 13 young healthy volunteers, painful heat stimulation was administrated to the right upper leg while performing single-voxel ^{1}H-MRS in a 3 T MR scanner with a short echo time of 20 ms and a repetition time of 3000 ms. GABA concentration increased 15% ($p < 0.02$) in a volume of interest placed in the rostral anterior cingulate cortex (rACC) [131]. In contradiction to the previous study (Mullins et al. 2005) the authors did not demonstrate any increase in glutamate or glutamine during the painful stimulation. The discrepancy between the findings can be explained by the partial overlap of Glu, the combined summed signal from glutamate, glutamine (Glx), and GABA at chemical shifts 2.0–2.5 ppm. Kupers et al. [131] used a user-independent fitting model (LC model) that fits non-overlapping resonances of GABA, Glu, and Glx, allowing for a better separation of the signal in the chemical shift regions, which might explain the differences between these findings. The rACC has reciprocal connections with thalamus [137]. The projection from thalamus to cingulate cortex is glutaminergic while the projection from the cingulate to the thalamus is GABA regulated [138].

Basal Cerebral Blood Flow by PET, SPECT, and Resting State fMRI (rs-fMRI)

PET and SPECT use injectable tracers to provide static measures of rCBF and thus directly infer neural activity. fMRI, which usually correlates rCBF with a reference signal such as painful stimulation, can be applied to measures of basal function with methods that evaluate temporal and spatial activity to establish functional interconnections. Functional connectivity MRI (fcMRI) correlates spontaneous fMRI fluctuations (<0.08 Hz) among multiple regions. This method is usually performed at rest (rs-fMRI) and the results contrasted between individuals, although the method can also be employed to assess the interconnections during painful stimulation. Technical aspects include the need to remove signal frequencies that correspond to heart rate and respiration, which requires assessment of electrocardiogram (EKG) and respiration during the scan. Most applications use a seeded analysis in which a particular brain locus such as posterior cingulate cortex is used as the baseline, reference signal. Correlations between the activity in this region and all other regions establish the regions that are "connected" to the seeded region. Additional brain networks are discovered by varying the seeded location. The choice of seed location is often based on a priori hypotheses. An interesting advance is the use of non-seeded analyses that require no a priori hypotheses and that reveal multiple independent networks. For example, the use of self-organizing maps (SOMs) and the use of independent component analysis (ICA) [139–145]. These "data-driven" approaches can find networks that were not predicted and would be missed if the critical seed was not selected. However, since these methods are essentially hypothesis-free, formal statistical testing is problematic.

Studies of rs-fMRI analyses of connectivity during the resting state have been used to define the "default mode" of cognitive processing; i.e., the normal activity present when not engaged in a task. Studies in healthy subjects have been used to define this network while comparisons between control and affected populations have demonstrated baseline differences in default mode processing. This approach identifies interconnections between brain regions but not the causal direction of these connections, the "effective" connectivity. A further step uses structural equation modeling methods to establish effective connectivity. For example, Labus et al. [90] evaluated PET images of functional images of 22 men and 24 women with irritable bowel syndrome (IBS) and showed that sex-related differences in brain activation were not due to mechanisms in visceral sensory afferents but mediated predominantly by emotional-arousal networks.

Fibromyalgia (FM)

The first functional brain imaging studies of FM used SPECT to examine rCBF in patients and control subjects with a

consistent finding of hypo-perfusion in the right thalamus and inconsistent results in other brain regions [146–148]. The few rs-fMRI studies to date have not yielded a consistent picture to be useful for clinical decision making [95, 145, 149]. Figure 17.3 illustrating functional magnetic resonance imaging (fMRI) responses to painful pressure applied to the left thumb in patients with fibromyalgia (FM) and healthy control subjects.

Chronic Fatigue Syndrome (CFS)

Similar to fibromyalgia, initial SPECT studies of CFS had conflicting results. The first two studies found different results, together showing altered perfusion in frontal, temporal, parietal and occipital cortices, and basal ganglia [150, 151]. The next found no differences [152]. In an analysis of basal activity by the maturing method of arterial spin labeling (ASL), Biswel et al. (2011) found decreased perfusion in

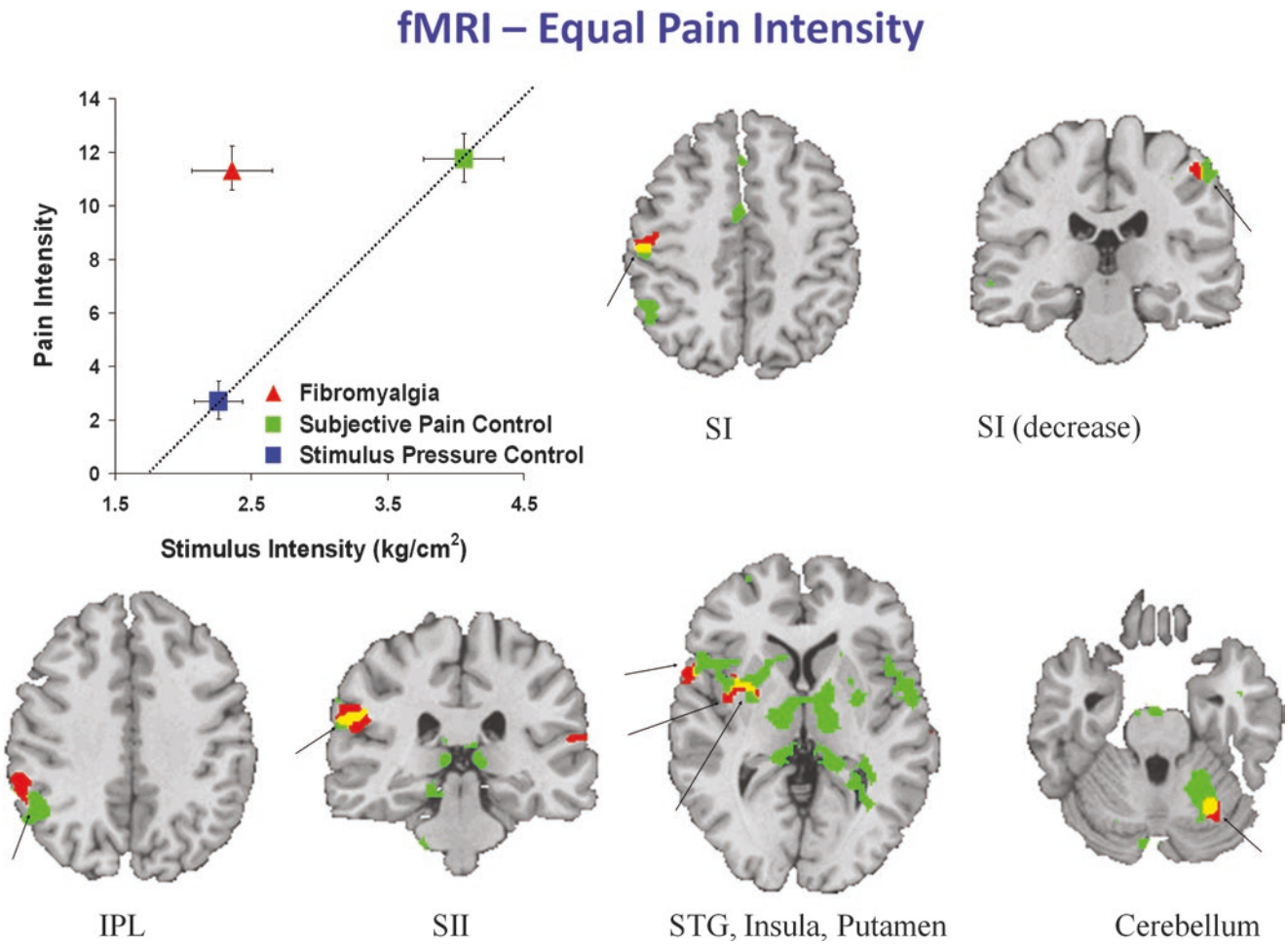

Fig. 17.3 Functional magnetic resonance imaging (fMRI) responses to painful pressure applied to the left thumb in patients with fibromyalgia (FM) and healthy control subjects. The top left graph shows mean pain rating plotted against stimulus intensity for the experimental conditions. In the *Patient* condition, a relatively low stimulus pressure (2.4 kg/cm^2) produced a high pain level (11.30 ± 0.90) shown by the triangle. In the *stimulus pressure control* condition, shown by the lower square, administration of a similar stimulus pressure (2.33 kg/cm^2) to control subjects produced a very low level of rated pain (3.05 ± 0.85). In the *subjective pain control* condition, shown by the upper square, administration of significantly greater stimulus pressures to the control subjects (4.16 kg/cm^2) produced levels of pain(11.95 ± 0.94) similar to the levels produced in patients by lower stimulus pressures. The remainder of the figure shows common regions of activation in patients (red) and in the *subjective pain control* condition (green), in which the effects of pressure applied to the left thumb sufficient to evoke a pain rating of 11 (moderate) is compared to the effects of innocuous pressure. Significant increases in the fMRI signal resulting from increases in regional cerebral blood flow (rCBF) are shown in standard space superimposed on an anatomical image of a standard brain (SPM96). Images are shown in radiologic view with the right brain shown on the left. Overlapping activations are shown in yellow. The similar pain intensities, produced by significantly less pressure in the patients, resulted in overlapping or adjacent activations in contralateral primary somatosensory cortex (SI), inferior parietal lobule (IPL), secondary somatosensory cortex (SII), superior temporal gyrus (STG), insula, putamen, and in ipsilateral cerebellum. The fMRI signal was significantly decreased in a common region in ipsilateral SI. (Reprinted with permission from Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional MRI evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum* 2002;46(5):1333–1343)

a large number of regions, with two patients showing the opposite of the group effect [153].

An interesting SPECT study compared 11 sets of monozygotic twins in which one twin met CFS criteria and the other served as a control [154]. No differences in perfusion were found. A non-SPECT study assessed perfusion with Xenon Computed Tomography. Non-depressed CFS patients showed reduced perfusion in a subset of preselected sites. The inconsistencies between all of these studies do not support a clinical utility for basal measurements in CFS.

Basal Cerebral Blood Flow by Arterial Spin Labeling (ASL)

Improvements in MRI technology, such as increased magnetic field strength and phase array receiver coils, enable arterial spin labeling (ASL), a non-invasive technique, to measure small changes in regional cerebral blood flow (rCBF) associated with pain. ASL can measure baseline perfusion at rest with the major advantage that unlike PET, SPECT, or fMRI perfusion, ASL does not require any injection of a tracer and since ASL is more stable over time the technique can be useful for the evaluation of long-duration interventions that require repeated measurements over time.

For further description of the Arterial Spin labeling technique, challenges, and post-processing methods please refer to Chap 3.

Evoked Pain in Healthy Control Subjects

In an ASL study of 14 healthy volunteers, subjects received alternating 1-min intervals of warm (35 °C) ("rest") and painful heat (48–50 °C) ("pain") applied to the left hand. In comparison of the pain and rest conditions, increased rCBF was found in bilateral insular, secondary somatosensory, and cingulate cortices and in the supplementary area (SMA) [155]. Unilateral changes were found in ipsilateral thalamus and in contralateral primary somatosensory cortex. The pain-related increases in rCBF were most notable in the bilateral insula, an area commonly activated in functional MRI studies involving pain. The average rCBF changes for all regions of interest were 3.68 mL/100 g/min, the average resting global CBF was 54 ± 9.7 mL/100 g/min.

A subsequent study with a similar approach demonstrated elevated rCBF to noxious stimulation in somatosensory cortex, anterior cingulate cortex, anterior insula, hippocampus, amygdala, thalamus, and precuneus, consistent with previous pain activation patterns using BOLD imaging [156].

Chronic Low Back Pain

An ASL study of patients with chronic low back and radicular pain compared with matched healthy normal subjects demonstrated that during periods of clinically significant worsening of the ongoing chronic pain there were significant increases in rCBF within brain regions known to be activated by experimental pain. These areas included somatosensory, prefrontal, and insular cortices and in other structures observed less frequently in experimental pain studies, such as the superior parietal lobule (part of the dorsal attention network). The authors noted that this effect was specific to changes in ongoing chronic back pain, but it was not observed after thermal pain application, or in matched, pain-free healthy controls [157].

PET Evaluation of Glucose Metabolism and Ligand Binding

Measures of brain activation based on rCBF (fMRI, SPECT, and PET) are inferences derived from a chain of events from neural activity to a hemodynamic response that can be influenced by extraneous factors ranging from vascular anatomy to factors that independently influence cerebral blood flow. Two PET methods avoid the use of rCBF as an intervening variable. One method more directly evaluates neural metabolism by measuring energy consumption using glucose metabolism. Using a labeled glucose tracer, [^{18}F]fluorodeoxyglucose (FDG), these methods assess neuronal activity over longer scan times of several minutes compared to 1 min for PET and 2 s for fMRI. This method has been used to provide evidence for the encoding of pain unpleasantness in insular cortex evoked in healthy volunteer subjects by application of acid buffers to skin and muscle [158] and to assess the cerebral mechanisms in the clinical condition of cluster headache [159].

One very useful and unique PET methodology uses specific radioligands to assess receptor occupancy and density In this approach, the tagged ligand competes with a compound of interest and the measure of "binding potential" (BP) reflects both the success of the radioligand in occupying the receptor (inverse of the occupancy by the target compound) and the number of available receptors to be occupied. Thus, depending on the experimental situation, a change in binding potential can be interpreted as a change in the concentration of the target compound or in up- or down-regulation of the receptor. The major applications of this approach to pain has examined the opioid system in the brain by the use of the specific mu-opioidergic agonist [(11)C]-carfentanil and the unspecific opioid receptor antagonist [(11)C]-diprenorphine. These methods have shown high levels of opioid receptor density in thalamus, prefrontal and cingulate cortex, basal ganglia and altered receptor occupancy in chronic pain conditions of rheumatoid arthritis, trigeminal neuralgia, and central poststroke pain [160]. The [(11)C]-carfentanil ligand has been used in experimental studies of tonic pain in healthy volunteer subjects that showed an

association with receptor occupancy and the magnitude of subjective evoked pain [161].

Fibromyalgia (FM)

The PET radioligand method has been used to compare opioid receptor availability in 17 patients with fibromyalgia and 17 control subjects [162]. In FM patients compared to controls, reduced binding potential of the radio-labeled opioid, [^{11}C]carfentanil was found in bilateral nucleus accumbens and left amygdala, and a trend ($p < 0.07$) in the right dorsal anterior cingulate cortex. This reduced binding potential suggests that the spontaneous pain of FM caused a release of endogenous and/or a reduced number of receptors, indicating a possible receptor down-regulation due to persistent occupancy of endogenous opioids. An analysis of individual results revealed a negative association between the binding potential in the left nucleus accumbens and affective pain ratings on the short form of the McGill Pain Questionnaire and negative association between the binding potential in the left amygdala and CES-D depression scores. These results support the group results and provide preliminary evidence for the application of these methods to individual cases.

At least two studies have avoided inferring neural activity by using PET to assess brain glucose metabolism in fibromyalgia. In 2004, Yunnus et al. used [^{18}F]fluorodeoxyglucose (FDG) PET in 12 fibromyalgia patients and 7 control subjects [163]. The results were negative, finding no difference in resting state between the patient and control groups. Positive results were observed in a within-patient study in which improvement in comprehensive treatment program was associated with a trend for significant increases in brain metabolism in limbic structures [164].

Irritable Bowel Syndrome (IBS)

IBS is characterized by altered bowel habits (either diarrhea or constipation predominant) and pain, with secondary symptoms of discomfort, bloating, and a sense of incomplete evacuation. IBS studies have also evoked these perceptions by inflation of a rectal balloon. IBS patients appear to be more sensitive, again described in terms similar to the clinical descriptions.

Hong et al. (2013) [165] used res-fMRI to compare IBS patients and healthy controls of both genders. Activity between brain regions was measured by computing the power in the frequency band of natural brain activity oscillations. The analysis found differences between genders regardless of the presence of IBS (females different than males in activity in the amygdala and hippocampus) and gender differences specific to IBS patients (insular and sensorimotor cortices).

These results suggest that any future clinical measure using this method must account for gender.

Temporomandibular Disorder (TMD)

TMD is the leading cause of orofacial pain, and this primary symptom is often accompanied by restricted jaw opening and joint noises, and by tenderness in muscles of mastication and in the neck. The initial rs-fMRI study of TMD found increased connectivity between several brain in a small sample of subjects ($n = 8$) and different connections were observed in a larger study ($n = 17$) [166, 167]. An additional rs-fMRI study comparing patients ($N = 23$) to controls ($n = 20$) found decreased connectivity in the left precentral gyrus, supplementary motor area, middle frontal gyrus, and right orbitofrontal cortex. A subsequent study from the same group of investigators comparing patients ($n = 30$) to 20 healthy controls reported reduced connectivity between the ventral striatum and ventral frontal cortices, between the dorsal striatum and dorsal cortices, and within the striatum. The decreased connectivity in these studies was interpreted as possibly related to decreases in behavioral function observed with TMD. Additional studies are needed to potentially support these interpretations by consistent findings.

Vulvodynia (VVS)

Vulvodynia or vulvar vestibulitis is a condition in which pain is experienced within the vulvar vestibule and may extend to adjacent non-vulvar regions. The pain may be provoked (tampon insertion, sexual intercourse) and/or may be experienced as ongoing, spontaneous pain. An elegant study uses rs-fMRI to assess resting state functional connectivity in patients with provoked VVS ($n = 29$) compared to both a group of healthy control subjects ($n = 20$) and importantly, to a group with another CPP condition, 29 patients with IBS [168]. The independent component analysis evaluated connectivity in three identified networks: sensorimotor, salience, and default mode. VVS patients showed clear differences in these networks compared to both normal and IBS control subjects. These alterations were associated with subjective VVS symptoms. This result suggests that features of provoked VVS may be specific to VVS and not shared with the spontaneous symptoms of other CPP conditions.

Anatomic Measurements of Gray and White Matter by Voxel-Based Morphometry (VBM)

Several fMRI methods evaluate anatomical properties of specific neuron classes that are likely related to function. These methods are discussed in detail in various chapter in part IV of this book. Briefly these measures distinguish between groups of neurons including cell bodies (gray matter) and the connection or wiring of these groups to other neuronal groups by bundles or tracts (white matter). Both white and gray matter volume can be measured at the voxel

level by voxel-based morphometry (VBM), which uses focal changes in brain structure as a functional measure. VBM performs a voxel-wise comparison of multiple MRIs of the brain and evaluates the volume of specific tissue and structures. For example, regional reductions in gray matter have been observed in chronic pain and stress-related disorders such as low back pain, tension type headache, chronic fatigue syndrome, and post-traumatic stress disorder [169–174]. These findings do not indicate causality, whether pain causes these brain changes or the alternative in which brain morphology represents a neurodegenerative disease that causes pain. A recent study of hip osteoarthritis supports the former concept that pain causes these changes. Gray matter loss in these conditions was partially reversed after surgical treatment that eliminated the pain [175].

Gray matter magnitude is referred to either as volume or density. These measures have been interpreted to indicate number of neurons, although they may measure changes in glial matter or other non-neuronal sources such as water content. Cortical thickness analysis (CTA) provides another measure of gray matter volume that measures the thickness of the cortical mantle.

Voxel-Based Gray Matter Morphometry (VBM) in Fibromyalgia (FM)

Kuchinad et al. reported a pronounced age-associated decrease in gray matter volume in FM quantified as 9.5 times the loss of gray matter observed in normal aging [176]. Whereas other studies did not demonstrate an overall reduction in total GM, but did find local decreases in GM in more specific regions such as middle cingulate gyrus (MCC) and anterior cingulate gyrus (ACC), insula, medial prefrontal cortex (MPFC), and lateral prefrontal cortex(PFC). Others have demonstrated increased GM volume in, for example, basal ganglia, lateral PFC, and insula [177]. A subsequent study found altered brain morphology near and partially overlapping with regions associated with pain modulation [178]. However, another study using both VBM and DTI found DTI to be more sensitive [179]. In addition, in 2009, Hsu et al. suggested that the observed changes in fibromyalgia may represent a simple confound, finding no differences when controlling for affective disorder [162, 180]. However, the observation of structural differences may provide information about the largely unknown mechanisms mediating this disorder.

Evaluation of Gray Matter in Chronic Fatigue Syndrome (CFS)

A study of 22 CFS patients found decreased gray matter volume in comparison to 22 healthy control subjects. This decrease was partially reversed in the lateral prefrontal cortex after cognitive behavioral therapy, supporting the concept that changes in gray matter volume can represent changes other than cell loss, such as glial cell volume [181]. Two studies showing no difference or reduced white matter volume in the occipital lobe also found reduced gray matter volume in the dorsal lateral prefrontal cortex [182] ($n = 16$), and in the parrahippocampal gyrus and in visual cortical areas ($n = 26$) [183]. An additional VBM study found increased gray matter volume amygdala and insula [184].

Evaluation of Gray Matter in IBS

Wallit et al. (2016) [95] summarized six studies of gray matter in IBS. These and a subsequent study [185] found gray matter reductions in basal ganglia and thalamus and in insular, prefrontal, anterior mid-cingulate, and anterior cingulate cortex. Many of these effects were observed in young girls, suggesting early alterations in brain development. These reductions in gray matter in IBS were counterbalanced by increased gray matter in a number of regions including cingulate, orbitofrontal and sensory/motor cortices with varying correlations to symptoms [95, 186–190].

These studies include several with very large number of subjects, with three studies ranging from 50 to 200 subjects [187, 189, 190]. Nevertheless, consistency sufficient for clinical utility has yet to emerge.

Evaluation of Gray Matter in Temporomandibular Disorder (TMD)

There are limited studies on VBM in TMD patients and the findings are, in part, contradictory. A VBM study in a small cohort of 9 TMD patients demonstrated decrease in gray matter volume in several areas; left anterior cingulate gyrus, right posterior cingulate gyrus, right anterior insular cortex, left inferior frontal gyrus, and in the superior temporal gyrus bilaterally [191]. Another study demonstrated cortical thickening in the primary somatosensory cortex frontal polar and the ventrolateral prefrontal cortex [192]. In the same study, the authors demonstrated a positive correlation between gray matter in the sensory thalamus and duration of disease, while cortical thickness in the primary motor and the anterior midcingulate cortices presented a negative correlation to pain intensity, and finally a negative correlation of pain unpleasantness to cortical thickness in the orbitofrontal cortex. Wilcox et al. demonstrated involvement of the brainstem especially within the medullary dorsal horn with significant decreased gray matter volume in the ipsilateral (to higher pain) spinal trigeminal nuclei both the nucleus interpolaris and nucleus caudalis as well as in region of the ipsilateral trigeminal principle sensory nucleus and in the rostral medullary raphe. There were no significant correlation to pain intensity or pain duration and the reduced gray matter volume [193]. Contradictory to these findings others have demonstrated increased gray matter volume in brainstem

trigeminal sensory nuclei, and in the thalamus. Increased gray matter volume compared to controls was also present in limbic regions such as the posterior putamen, globus pallidus, and anterior insula. The only area with decreased gray matter volume compared to controls was located just posterior to the central gyrus in the primary somatosensory cortex [194].

Diffusion-Weighted Imaging (DWI)

Diffusion-weighted imaging (DWI) measures the mobility of water molecules and is described using a scalar parameter—the diffusion coefficient D. The most widely used diffusion-weighted image acquisition method is single-shot echo-planar imaging (EPI). The use of motion-corrected multi-shot EPI and sensitivity-encoding EPI techniques have improved image resolution and reduced distortion.

Diffusion Tensor Imaging (DTI)

Diffusion tensor imaging (DTI) yields quantitative measures reflecting the integrity of white matter fiber tracts by taking advantage of the intrinsic properties of directionality of water diffusion in human brain tissue. Brownian motion characterizes the general diffusion of water molecules. When water molecules are unconstrained, the direction of motion of a given molecule is random, described by a Gaussian distribution of displacement of water molecules over time. DTI of water is probed by application of diffusion-sensitization gradients in multiple directions. Appropriate mathematical combination of the directional diffusion-weighted images provides quantitative measures of water diffusion for each voxel via the apparent diffusion coefficient (ADC), as well as the degree of diffusion directionality, or anisotropy, which can be measured by fractional anisotropy (FA) (Fig. 17.4a–c). The principal diffusion direction of the brain structure to be examined can be encoded with color, resulting in color-coding maps or directionally encoded FA maps (DEC FA maps). In these color-encoded maps the fibers have been given different colors (red, green, and blue) depending on their different diffusion directions [195] (Fig. 17.4d).

For further description of the diffusion weighted imaging and the diffusion tenor imaging principles, technique, challenges, and post processing methods please refer to Chaps. 1 and 39.

DTW and DTI Applications to White Matter Evaluation in Pain

Neuropathic Pain

There are few reports of DWI and DTI evaluation of pain conditions [196, 197]. Gustin et al. [196] used diffusion tensor imaging to study neural changes in 11 spinal cord injury (SCI) patients without pain, 11 SCI patients with pain, and 45 healthy subjects with no spinal cord injury. Results showed significant changes in mean diffusivity (MD) in pain-related regions as well as in regions of the classic reward circuitry. Increased MD was found in right posterior parietal cortex (PPC), right DLPFC, left anterior insula, medial orbitofrontal cortex, and the premotor cortex while decreased MD was present in ventral midbrain, left amygdale, and right ventroposterior (VP) thalamus in SCI patients with pain compared to SCI without pain, with the clusters in or immediately adjacent to gray matter. There were a positive correlation between pain and the MD values in DLPFC, PPC, anterior insula, and in premotor cortex and a negative correlation between MD values and pain intensity in the amygdale, and VP thalamus in the SCI patients. Analysis of individual subjects showed that the MD values in the SCI patients regardless of pain or no pain were within the range of the MD values of the control subjects with the exception of (1) VP thalamus and (2) amygdale. In the VP more than 90% of the SCI pain patients had MD values below the low-

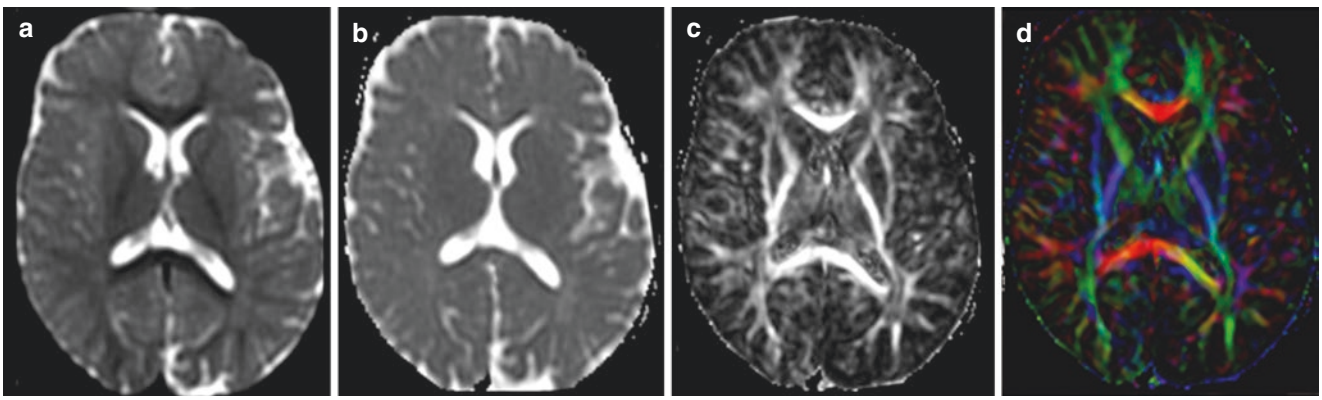

Fig. 17.4 Axial T2-weighted (**a**), ADC (**b**), FA (**c**), and directionally encoded FA map (**d**) at the level of the basal ganglia in healthy volunteer

est MD in control subjects; and in (2) the amygdale, more than 80% of the SCI pain patients had MD values below the lowest MD value in the control subjects. The authors speculate that thalamic and amygdala anatomical differences reflect changes as a consequence of the injury itself while the changes present in the other regions may reflect pre-injury values that predispose an individual to the development of persistent pain following a traumatic event such as SCI.

Temporomandibular Disorder (TMD)

A few studies have been published on white matter microstructure in TMD and the results do not present coherent evidence for microstructural changes in the TMD patients [191, 192]. One study demonstrated that widespread reduction in FA was present in corpus callosum (CC), internal and external capsule, in tracts associated with the thalamus and in primary somatosensory cortex (SI) and between the genu of the CC and the DLPFC. This study also demonstrated increased connectivity between the CC and the frontal pole [192]. Microstructural changes have also been demonstrated in the brainstem. Increased mean diffusivity have been seen in region of the ipsilateral (to highest pain) medullary dorsal horn and SpV especially in the SpVc and bilaterally in region of the trigeminal nerve in the pons, the midbrain periaqueductal gray matter. Notably no regions demonstrated any increased or decreased FA. In addition, the study could not demonstrate any correlation between these microstructural changes and pain duration or pain intensity as well as no correlation to reduced gray matter volume in these regions [193]. In the same study, diffusion tensor tractography demonstrated lower FA values and increased mean diffusivity in the root entry zone of trigeminal nerve, lower FA values in the spinal trigeminal tract, and in the ipsilateral and contralateral ventral trigeminothalamic tracts. Similar findings were also seen in the contralateral tracts. This in contrast to findings seen in patients with trigeminal neuropathy in whom no significant differences in diffusivity measures in the root entry zone of the trigeminal nerve, the spinal trigeminal tract, or the ventral trigeminothalamic tract were present.

Fibromyalgia (FM)

There are a limited number of DTI studies in FM and no consistent findings have been found [179, 198–200]. In one of the few studies of DTI in pain conditions, 19 patients with FM and 25 healthy controls with no pain were examined to investigate whether DWI and DTI can depict cerebral abnormalities in fibromyalgia patients and to test for significant differences in measured ADC histograms between these patients and normal controls [200].

The FA values were significantly lower in the right thalamus in the FM patients compared with those obtained in healthy controls (mean [SD] FM: 0.258 (0.022); HC: 0.278 (0.035); $p = 0.02$). A negative correlation was found between the FA values in the right thalamus and clinical pain ($r = -0.50$, $p = 0.049$) in the FM group, indicating that those individuals with worse clinical pain had a lower value. A negative correlation was observed between the FA values in right thalamus and the belief in "external" pain control ($r = -0.72$, $p = 0.005$) in the FM group, indicating that these low right-thalamic FA values were also significantly associated with a cognition known to be negatively associated with prognosis in chronic pain. Similar findings of decreased FA in the thalamus have been found in another study [179].

No differences in whole brain diffusivity were noted between the two groups. The magnitude of these differences was statistically greater in those individuals with worse clinical pain and an external locus of pain control, and non-significantly associated with other clinical parameters of disease severity. These findings are in agreement with previous studies utilizing SPECT [147, 148] and MR perfusion [201], suggesting that these findings might be clinically relevant rather than spurious findings. The precise cause for these abnormalities is unclear. Because of the focal nature of these findings, and other accumulating evidence regarding fibromyalgia, it is not likely that the abnormalities identified in this study are due to an ongoing demyelization or even axonal injury, but instead are more likely the result of neuronal dysfunction. In another study, significantly decreased FA was present in both thalami, the thalamocortical tracts, and in both insular regions. Increased pain intensity scores were correlated with changes in DTI measurements in the right superior frontal gyrus, and high intensity scores for stress symptoms were correlated negatively with diffusivity in the thalamus and FA in the left insular cortex [179]. A recent study demonstrated findings of reduced FA that correlated with increased pain in regions of the corpus callosum that connects to the primary somatosensory cortex [199].

White Matter Perfusion Using Contrast-Based and ASL Imaging in Fibromyalgia (FM)

Conventional contrast-enhanced MR perfusion has been used to evaluate changes in fibromyalgia patients [125]. In that study 26 FM patients and 21 age-matched control subjects were studied with pre- and post-contrast enhanced conventional brain MRI on a 1.5 T magnet as well as a contrast-enhanced perfusion sequence. Multiple circular 100 cm^2 regions of interest (ROI) were placed in selected bilateral brain gray and white matter structures. The mean time to enhance (MTE) and negative enhancement integral (NEI) for each region were obtained. Parietal white matter was used as a perfusion baseline to calculate ratios for each measured region. The authors found that the relative NEI values were significantly lower in the right thalamus ($p = 0.016$) and significantly higher in the right dorsal lateral prefrontal subcortical white matter ($p = 0.018$) for FM patients compared to healthy controls. A trend toward lower

NEI values in the left thalamus was also observed ($p = 0.059$). The decrease in relative NEI in the right thalamic regions is consistent with previously reported SPECT and PET data. The increased NEI values in the right dorsal lateral prefrontal subcortical white matter might be of interest for future investigations as previous MR spectroscopy studies have demonstrated changes in this region as well [107]. Our laboratory has performed a preliminary study of perfusion in fibromyalgia using ASL. In a basal design comparing rCBF in eight patients with fibromyalgia and seven healthy control subjects, we found decreased rCBF in the bilateral thalamus in patients in comparison to control subjects (Hernadez, unpublished observations), a result observed previously for fibromyalgia [125, 147, 148, 202, 203] and other painful disorders such as traumatic peripheral neuropathy [204] and metastatic breast cancer [205].

Evaluation of White Matter in Chronic Fatigue Syndrome (CFS)

Studies of white matter volume using VBM have found either no difference in 19 CFS patients [182], decreased volume in the occipital lobe in 26 patients [183], or decreased volume in the midbrain and brainstem [184]. White matter loss was also found during autopsy in a patient diagnosed with CFS [206].

Evaluation of White Matter in IBS

Several studies have used diffusion tensor imaging (DTI) to assess white matter integrity in IBS. Increased FA was observed adjacent to the insula ($n = 10$) [207] and in or adjacent to MPFC and corpus callosum (=33) while decreased FA was observed in or near the thalamus, basal ganglia, sensory motor cortex, and posterior commissure [208]. In a large study of 66 IBS patients and 23 healthy control subjects, multiple regressions evaluated the predictive power of DTI results among other variables such as age, sex, and cortical thickness [209]. The mean FA of white matter bundles innervating visceral regions of primary somatosensory cortex significantly predicted diagnosis. A subsequent large study of 65 IBS patients and 67 healthy controls evaluated a measure of symmetry between right and left hemispheres, termed interhemispheric voxel-mirrored homotopic connectivity (VMHC) [210]. This measure was higher in IBS patients in a large number of brain regions and lower in a few brain regions. The authors conclude that these results provide evidence of disrupted functional coordination between hemispheres in the cortical-thalamic circuit in IBS. A recent study also used DTI to assess white matter integrity in 19 IBS patients and 20 healthy controls. In addition to the FA parameter which is a ratio of axial diffusivity (AD) and radial diffusivity (RD), these authors examined differences in all three measures and in a fourth measure of mean diffusivity (MD). A number of significant different differences were reported for FA, AD, and MD which was interpreted as possible axonal injury and loss [211].

Evaluation of Gray Matter in VVS

Schweinhardt et al. (2008) [212] evaluated 14 young women with a 1–9 year history of vulvar pain and 14 control subjects. The vulvar pain group showed significantly greater gray matter densities in parahippocampal gyrus, hippocampus, globus pallidus, caudate nucleus, and substantia nigra. In contrast, studies of older subjects with chronic pain showed gray matter decreases in these regions, suggesting a transition over time. In a subsequent study, women with provoked vestibulodynia (pain on penetration such as during intercourse or tampon insertion) were classified as primary (pain since first penetration) and secondary (acquired later) [213]. Primary patients showed significant gray matter decreases in pain-related areas, which could be interpreted in terms of "aging" or multiple evoked-pain mechanisms.

Anatomical Measures of Gray and White Matter

Increasing evidence demonstrates alterations in gray and white matter in many of the CPP syndromes that could reflect either causal processes or consequences of pathology. Findings such as differences between and within syndromes, and varying associations with symptoms suggest a potential for clinical utility and a need for considerable more research before using these measures to aid diagnosis or treatment planning.

Conclusion: Future Considerations

After the initial PET studies of baseline brain activity, the field of pain neuroimaging was dominated by a large number of fMRI studies of evoked pain responses. Averages of group responses have provided important information about mechanisms of pain processing. Many mechanisms of pain are poorly understood and many pain conditions are poorly diagnosed and treated. More recent neuroimaging studies have used methods in resting individuals, without stimulation, that may provide relevant information about chronic pain conditions. Many of these methods have also been used to assess pain mechanisms using group averaged data. These studies include also the emerging field of pharmacological fMRI that assesses the mechanisms of pain treatments. Unfortunately, this accumulating body of important evidence is not immediately useful for the clinical problems of diagnosis, treatment choice, and monitoring treatment efficacy.

This need provides an important future direction for all of these imagining modalities.

Certain imaging modalities are closer to the goal of individual evaluation. We have highlighted the methods of MR spectroscopy and diffusion imaging because these methods are already used in the clinic and already bridge the gap from the laboratory to the clinic. Many of us in the research field have received calls from patients asking for an fMRI to validate their pain. We have replied that the methods are not sophisticated enough yet to be informative for an individual case, but that we are working on the problem. It is now time to work a little harder and target the difficult challenge of validating functional neuroimaging for clinical case decision.

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