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INVITED REVIEW

Central Mechanisms of Pain Revealed Through Functional and Structural MRI

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Abstract MR-based brain imaging technologies provide a suite of functional and structural metrics that can be used to test hypotheses about the CNS mechanisms underlying pain perception and chronification, from a cellular level to a systems level. Two types of functional MRI discussed in this review provide insight into pain mechanisms: stimulus-evoked fMRI and task-free ("resting state") fMRI. The former can assess how the brain responds to noxious or non-noxious stimuli normally or in a chronic pain state as a window into understanding pain, hyperalgesia and allodynia. The latter can assess functional connectivity reflecting synchronous ultra-slow frequency oscillation between brain areas. This provides insight into how brain areas work together as networks to produce pain and how these networks may be modified due to chronic pain. Perfusion MR (e.g., arterial spin labeling) can also provide task-free information pertaining to ongoing brain activity that may reflect spontaneous (ongoing) chronic pain. Structural MR techniques can be used to delineate gray and white matter abnormalities and markers of neuroinflammation associated with chronic pains. Functional and structural MRI findings point to brain and peripheral nerve abnormalities in patients with chronic pain, some of which are pre-existing and others that develop with prolonged pain (and related neuroinflammation) over time. Recent studies indicate that some structural brain abnormalities associated with chronic pain are reversible following effective pain treatment. These data together with findings from studies of individual differences suggest that some chronic pains arise from a combination of pre-existing vulnerabilities and sustained abnormal input.

Keywords Pain · MRI · Gray matter · White matter

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Introduction

The pain experience is complex and classically considered to include two major components (Casey 1982): the sensory-discriminative component is for localizing and feeling specific attributes of pain, and the affective-motivation component comprises the emotional and cognitive aspects of the experience. There is also a third, motor component that is important to mount a response to the pain. Each of us can experience pain somewhat differently. Furthermore, the pain experience can also vary depending on the evoking stimulus and context. The individual and situational variability is in part due to innate biological factors, and in part due to external and experiential factors (i.e., "nature and nurture"). The brain mechanisms responsible for pain are thus complex and not necessarily static. We now know that brain structure and function are plastic and can adapt or maladapt to conditions such as prolonged nociceptive input, as may be the case for chronic pain. Human neuroimaging can reveal the location and characteristics of brain responses to acute pain and plasticity associated with chronic pain. This review will provide an overview how MRI-based imaging techniques are being applied to study the central pain system under normal conditions and in chronic pain states. We will also discuss the technological advances in imaging that are now revealing aspects of neuroinflammation in relation to chronic pain.

A model of acute and chronic pain

Pain is thought to be due to complex central processing of ascending (incoming) signals and shaped by descending modulatory pathways. The main ascending pain pathway is the spinothalamic tracts that roughly distributes into a lateral sensory-discriminative and a medial affective system (Albe-Fessard et al. 1985; Willis 1997). Division of function is less clear in the cortex where pain processing is thought to occur in a distributed network (Treede et al. 1999) including primary and secondary somatosensory cortex (S1, S2) (Berkley and Parmer 1974; Kenshalo and Isensee 1983; Chudler et al. 1986; Chudler et al. 1990; Kalliomäki et al. 1993; Dong et al. 1994; Brüggemann et al. 1997; Kenshalo et al. 2000), anterior and mid cingulate cortex (ACC/MCC) (Vogt et al. 1993; Devinsky et al. 1995) and insula (Dostrovsky and Craig 1996; Augustine 1996). Imaging studies of pain report activations in multiple brain regions, including S1, S2, ACC/MCC, insula, prefrontal cortex (PFC), cerebellum and supplemental motor area (SMA) (Peyron et al. 2000; Derbyshire 2003; Strigo et al. 2003; Apkarian et al. 2005).

Cortical networks subserve multiple functions including sensory-discrimination (S1, S2), motivation-affect (ACC/MCC, insula, PFC), motor (SMA, cerebellum), and also attention, arousal and response selection/emotion functions (ACC/MCC, PFC, S2) (Treede et al. 1999; Peyron et al. 1999; Peyron et al. 2000). Neuroimaging has revealed that the activity evoked by pain and attention-demanding tasks (including those requiring response selection) is typically located in remarkably similar regions of the anterior- and mid-cingulate regions (Torta and Cauda 2011), leading to the concept that these regions play a role in general salience detection (Downar et al. 2003) (see below). For example, the insula is involved in many sensory and cognitive functions (Augustine 1985; Craig et al. 1994; Craig 1995; Craig et al. 1995; Augustine 1996; Craig and Dostrovsky 1997), including pain (Burton et al. 1993; Schneider et al. 1993; Coghill et al. 1994; Hsieh et al. 1995; Casey et al. 1996; Craig et al. 1996; Svensson et al. 1997; Davis et al. 1998). The cingulate cortex comprises a rostral affective (ACC) and mid cognitive division (MCC) (Bush et al. 2000) and nociceptive neurons have been identified in the human MCC (Sikes and Vogt 1992; Hutchison et al. 1999). However, this area of the cingulate cortex also contains neurons responsive to attention-demanding, cognitive and emotional stimuli (Davis et al. 2000; Davis et al. 2005) and responses to pain in this region may actually represent a general salience response (Downar et al. 2003). Indeed, there is now converging evidence to suggest that the MCC and other cortical areas (e.g., temporoparietal junction, dorsolateral PFC (dlPFC), insula) are involved in multiple functions many of which are actually invoking a non-specific salience response (Downar et al. 2002; Legrain et al. 2010; Torta and Cauda 2011; Liang et al. 2012). Indeed these regions form a functionally-coupled network that consistently responds to salient stimuli. Descending pathways from the cortex (e.g., DLPFC; ACC) to the brainstem and spinal cord (Bingel and Tracey 2008) modulate the impact of ascending signals and the pain experience.

A model of acute pain and central abnormalities in chronic pain is shown in Fig. 1. The main concept is that pain is related to activity in areas of the brain that contribute to the overall sense and intensity of pain, and areas that contribute to its salience, affect cognitive behaviours and trigger the descending pain modulation pathway. However, focal areas of activity (represented by the boxes) do not operate in isolation but through connections (indicated by the lines between the boxes) between complex networks.

There can be 2 types of connectivity between brain areas: anatomical white matter connections, and functional associations of synchronous activity between areas (via interconnections or common inputs). Networks related to attention can interact with the networks that subserve various nociceptive functions. Because of the inherently salient nature of pain, some brain areas reside in both pain and attention networks.

In a chronic pain state, there may be abnormal pain- and/or salience/attention-related activity, disturbances in connectivity (functional, anatomical) and/or morphology of the pain, attention, and descending pain control networks as well as other networks (see below). Abnormalities may represent pre-existing vulnerabilities or arise from disease/pain-driven plasticity. Although our model focuses on forebrain processes, there may also be peripheral abnormalities that also contribute to the chronicity of pain. Many chronic pains are characterized by spontaneous pain, cognitive/attention deficits, and signs of deficient descending controls that may arise from a combination of pre-existing factors and disease-driven plasticity.

Most models of chronic pain focus on neuronal abnormalities, but it is becoming increasingly apparent that glia function needs to be considered in models of chronic pain (Chiang et al. 2011). This is not surprising given that there are many more glial cells in the nervous system than there are neurons. For example, in the periphery, satellite glial cells in dorsal root ganglia and trigeminal ganglia have been shown to play a role in peripheral nociceptive conduction and transmission. In the CNS, microglia and astroglia contribute to sensitization and chronification of pain (Chiang et al. 2011) but are not involved in normal nociceptive processing (Watkins et al. 2001; Milligan and Watkins 2009). Furthermore, microglia are also activated after inflammation and so likely are involved in pain arising from CNS inflammatory processes (Chiang et al. 2011).

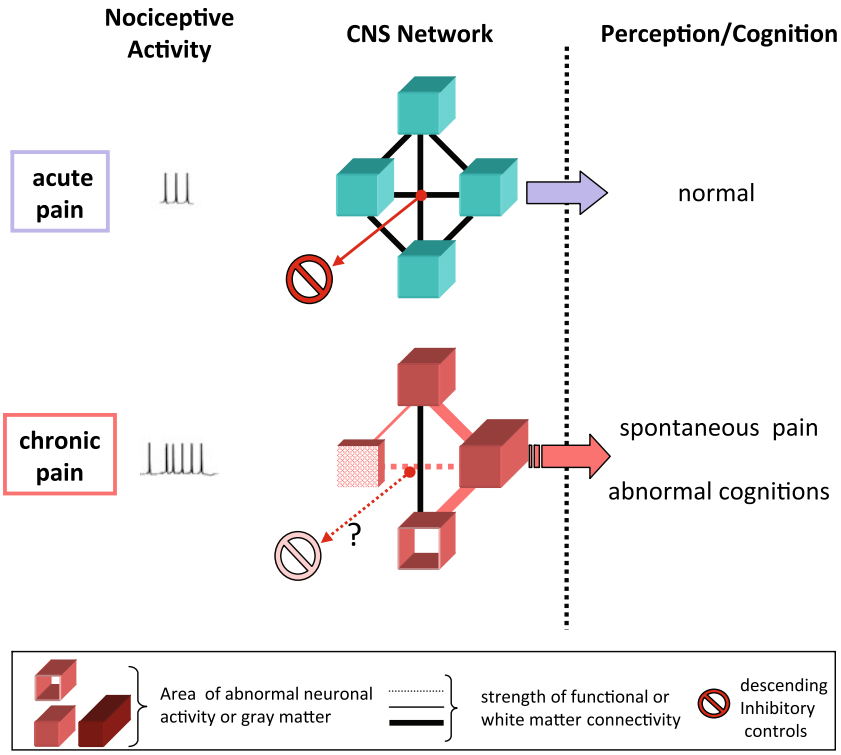

Fig. 1 A model of acute and chronic pain. Top: Non-pathological acute pain is associated with neuronal activity in pain-signaling neurons. The multidimensional nature of pain is reflected by activity within multiple brain regions that operate as networks, and also induce engagement of descending anti-nociceptive pathways. Bottom: In a chronic pain state, there can be aberrant or ectopic prolonged neuronal activity in nociceptors, and CNS networks that subserve pain and attention/cognition functions. Brain plasticity in chronic pain states may also involve altered network functional or structural connectivity as well as gray matter changes, and an abnormal descending inhibitory control system. (modified from (Davis et al. 2011))

MR-based neuroimaging technologies used to test pain models

Developments in neuroimaging technologies now provide an opportunity to test models of acute and chronic pain like the one depicted in Fig. 1. The attributes of the pain system described in this model can be examined with seven types of functional and structural neuroimaging technologies to assess: 1) Brain responses to a noxious stimulus (stimulus-related functional MRI); 2) Brain responses related to a specific pain experience (percept-related functional MRI); 3) Functional connectivity between specific brain areas, and in networks ("resting state" functional connectivity with functional MRI); 4) Neuronal activity as reflected by regional cerebral blood flow (arterial spin labeling perfusion MRI); 5) Gray matter volume and cortical thickness (structural MRI); 6) White matter integrity and putative markers of neuroinflammation (diffusion tensor imaging); 7) White matter connectivity between brain areas (diffusion weighted imaging/tractography). The basic principles of these technologies and their applicability to pain research are described below.

Functional MRI of pain

Functional MRI (fMRI) signals are based on hemodynamics and so provide an indirect measure of brain activity. The two main types of information that can be derived are 1) responses to a stimulus, task, or related to a perception such as pain, and 2) synchrony between brain areas in a task-free state.

Brain responses to a noxious stimulus

The most common type of fMRI studies evaluates brain responses that are linked to the presentation of an experimental stimulus in comparison to a baseline or control stimulus. This approach can be used to determine how healthy individuals respond to painful stimuli and how individuals with chronic pain respond to either noxious or innocuous stimuli. Therefore, these studies provide a window into the brain mechanisms underlying acute pain and also stimulus-evoked pains (e.g., hyperalgesia and allodynia) in individuals suffering from chronic pain.

Stimulus-evoked fMRI studies evaluate blood oxygen level dependent (BOLD) signals that are related to the proportion of oxy- to deoxy-hemoglobin in the blood (Ogawa et al. 1990). Most fMRI studies of pain use a block design whereby the noxious stimulus is applied for blocks of 10–30s interspersed with blocks of the control condition. The BOLD hemodynamic response function (HRF) is rather slow, peaking about 4–6 after a brief stimulus and lasting approximately 10–14 s (see Fig. 2). Thus, to identify the noxious stimulus-evoked brain response, first a predictor function is derived that reflects the timecourse of the noxious stimulus delivery mathematically convolved with the HRF to account for this slow, dispersed response. The predictor function is then used to

determine whether a brain area shows a "response", essentially a statistically significant difference in the BOLD signal during the time a stimulus is delivered compared to when a control stimulus is delivered (or during a baseline period).

Numerous studies of pain have used this standard approach and have found that acute pain stimuli evokes activity in widespread brain regions including the S1, S2, ACC, MCC, and insula (Apkarian et al. 2005). Some fMRI studies have also reported that noxious stimuli evoke activity in additional brain areas such as the PFC, the motor cortex, the SMA, and subcortically in the basal ganglia, thalamus and brainstem (Apkarian et al. 2005; Duerden and Albanese 2011). In general, the myriad of findings indicates that pain is associated with activity across distributed areas of the brain, in regions not only traditionally part of pain pathways, but also in areas implicated in innocuous somatosensory, cognitive and motor functions. These findings have led to a broadening of the original concept of pain with the recognition that the pain experience is comprised of affective, emotional, attention, motor responses to noxious stimuli in addition to the pain sensation itself.

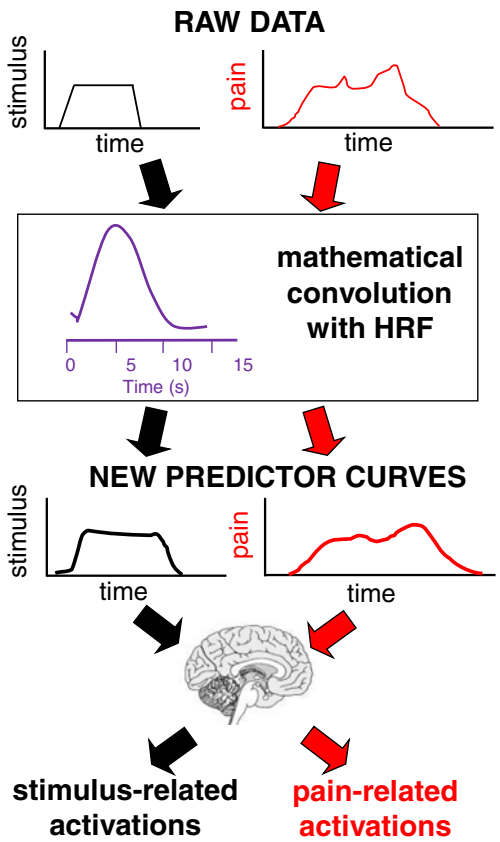

Fig. 2 Stimulus-evoked and percept-related fMRI. Two approaches to fMRI study design involve interrogation of data for activations related to the timecourse of the stimulus delivery (left) or related to the timecourse of a particular sensation evoked by the stimulus, such as pain (right). The percept-related approach requires the subject to provide online continuous ratings of their perceptual experience

Brain responses related to a specific pain experience (percept-related responses)

For many sensory systems, the sensations occur in a time-locked fashion with the delivered stimuli. However, this is not always the case for pain. For example, different types of acute pain qualities show varying temporal features (Davis and Pope 2002), some attenuating during a sustained stimulus and other increasing gradually over time (Hashmi and Davis 2008). There are also sex differences in pain adaptation to sustained stimuli and habituation to repeated stimuli (Hashmi and Davis 2009). Furthermore, pain responses in chronic pain patients can be quite dissociated from the time-course of the noxious stimuli, often lingering well after the noxious stimulus has been terminated (Kwan et al. 2005a). Therefore, the simple approach of stimulus-related fMRI analysis described above is not suited to locate brain responses that reflect specific pain percepts or pains that change with sustained or repeated stimuli. To address this shortcoming, we and others developed an approach known as "percept-related" fMRI (Apkarian et al. 2001; Davis et al. 2002; Davis et al. 2004; Porro et al. 2004; Kwan et al. 2005b; Davis 2006) (Fig. 2). This approach is designed to identify brain responses that reflect the temporal pattern of a specific percept. The key methodological necessity in percept-related fMRI is to know precisely what percept the subject is experiencing, and the exact timing of when the subject is experiencing it. The most precise way to track such an experience is to acquire continuous online percept ratings during MRI acquisition. These ratings can then be used to create HRF predictors that reflect the subject's personal experience.

For example, we used this percept-related fMRI approach to extract and distinguish brain responses linked to noxious cold-evoked prickle sensations (Davis et al. 2002). We found prickle-related activity in the MCC, ACC, insula, S2, PFC, premotor cortex, as well as the caudate nucleus and dorsomedial thalamus, and attribute these findings to brain activity related to the painful prickle quality itself and also to the sense of something moving on the skin, the inherent salience of the percept, and the desire to mount a motor response. This same stimulus evoked paradoxical heat sensation-related responses in the anterior /mid insula that was proposed to represent thermal perception (Davis et al. 2004).

The utility of percept-related fMRI is also apparent from our findings of disparate brain responses linked to rectal distension pressure stimuli versus those linked to rectal pain sensations in both healthy subjects and patients with irritable bowel syndrome (Kwan et al. 2005b). The percept-related approach was critical for this study because healthy subjects experience rectal-evoked pain that is time-locked to the rectal stimuli, but patients with irritable bowel syndrome

have intense rectal-evoked pain that is not time-locked to rectal distension stimuli (Kwan et al. 2005b). In particular, we found that rectal distension-evoked pain readily activated the ACC and anterior insula in healthy subjects but not in this patient group. The lack of pain-evoked ACC and insula responses in the patients could be due to the reduced gray matter that we subsequently found in these regions and the functional coupling between these areas (Davis et al. 2008; Taylor et al. 2009; Blankstein et al. 2010) (see below). Overall, these abnormalities in the patients may reflect their heighted rectal-evoked pain that could arise from reduced brain responses to detection salient, painful interoceptive stimuli and triggering of antinociceptive and homeostatic mechanisms.

Functional connectivity between brain areas

Rather than assessing evoked responses, it is also possible to measure neural activity that is not linked to a specific stimulus or task. The most developed approach is referred to as "functional connectivity" and identifies brain regions that have synchronous ultra-low frequency oscillations (<0.1 Hz). This approach provides insight into how brain areas work together as networks to produce pain and how these networks can become strengthened or weakened in chronic pain (Fig. 3).

It is important to appreciate that the term "functional connectivity" refers only to the finding that brain areas show temporal correlation at <0.1 Hz (Friston 1994). Thus, the association between areas that show functional connectivity may be via direct connections, indirection connections, or through a common input. Functional connectivity has been used to examine putative networks of brain areas that show intrinsic connectivity, typically identified in a "resting state" when the subject is not engaged in a task. The first network shown to have functional connectivity was deemed to represent a *default* mode of the brain (the DMN) (Raichle et al. 2001; Gusnard et al. 2001; Mazoyer et al. 2001) and includes the posterior cingulate, precuneus, medial PFC (mPFC) and lateral parietal cortices. These areas were active and showed functional connectivity in a task-free state, but were suppressed during a task (i.e., task-negative activity), hence the proposal that the network functions as an internal and external environmental monitor (Greicius et al. 2003; Greicius and Menon 2004; Fransson 2005). Other functionally connected networks that become active during a task can show anti-correlated activity to the default mode network (Fox et al. 2005). In general, intrinsic networks are readily identifiable in healthy humans, and functions have been proposed based on the spatial constellation of regions that are functionally connected (Smith et al. 2009), and their

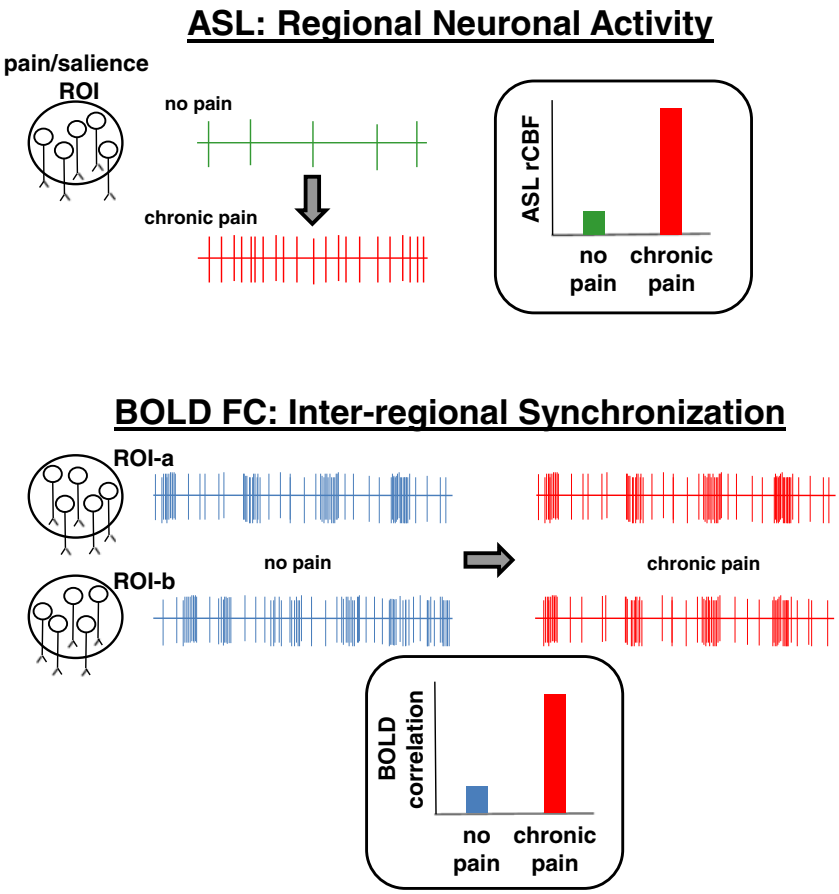

Fig. 3 Chronic pain-related brain activity. Top: Pain is signaled by increased neuronal activity (action potentials represented by vertical ticks) in neurons located in specific brain areas associated with pain and salience. The technique of arterial spin labeling (ASL), a perfusion-based MRI application, can be used to detect increased rCBF associated with this ongoing activity within a specific brain region of interest (ROI). Bottom: Pain may also increase the neuronal synchronization (seen in low frequency oscillations) between ROIs in a network, and this can be detected with resting state BOLD fMRI

co-activation during a task. For example, several intrinsic resting state networks have been identified (Fox et al. 2005; De Luca et al. 2006; Weissman-Fogel et al. 2010) that may serve salience, executive control, sensorimotor, cognitive and emotional functions.

It is likely that interactions between intrinsic resting state networks and networks of brain areas that receive nociceptive input become dysfunctional in pain states. For example, we and others have found that the DMN is suppressed by both cognitive load and acute pain (Seminowicz and Davis 2007b) and disrupted in chronic pain (Baliki et al. 2008). In the context of chronic pain, two recent studies have identified abnormal DMN connectivity. One study reported increased connectivity of the mPFC with pain-related regions (e.g., insula, S2, MCC) in chronic low-back pain (Baliki et al. 2011). Another study reported greater DMN connectivity with the insula in fibromyalgia (compared to controls) that was related to pain intensity (Napadow et al. 2010). In a follow-up study of the same patients, this group (Napadow et al. 2012) found that DMN connectivity with the insula was reduced proportionally to the reduction of their pain. Another study identified increased insular-cingulate connectivity in myofascial temporomandibular disorder patients during rest (Ichesco et al. 2012). Furthermore, the mPFC, as part of the DMN, is deactivated (an abnormal response) during task performance in chronic pain (Baliki et al. 2008), including temporomandibular disorder (Weissman-Fogel et al. 2011). Patients with chronic pain may be in a "stuck" state of self-referential thought or focus on their pain, and this state may relate to their abnormal intrinsic brain networks.

Functional connectivity can also be used to interrogate patterns of brain connectivity with focal brain regions-of-interest ("seed") (Fig. 4). With this seed-based approach, a "fingerprint" of connectivity can be defined for one brain area. For example, we and other groups have created connectivity fingerprints for subregions of the insula (Taylor et al. 2009) and cingulate cortex (Margulies et al. 2007; Yan et al. 2009; Yu et al. 2011). Our finding of functional coupling between the MCC and anterior and mid-insula provides a framework for understanding the parallel abnormal responses of these regions to rectal distension in patients with irritable bowel syndrome, as mentioned above (Kwan et al. 2005b). Interestingly, another study has shown that reduced insula-PAG functional connectivity in individuals with high pain vigilance (Ploner et al. 2010). This supports the concept that an attenuated insula response in patients with irritable bowel syndrome who have a strong focus (vigilance) on their pain, would also be coupled to reduced activity in the PAG descending antinociceptive system.

Neuronal activity as reflected by regional cerebral blood flow

Arterial spin labeling (ASL) is a perfusion MRI technique that can provide task-free information pertaining to ongoing brain activity that may reflect spontaneous pain characteristic of chronic pain populations (Fig. 3). ASL is akin to ^{15}O-PET in that it can produce quantitative images of regional cerebral blood flow (rCBF) which reflects neuronal activity with or without a task or stimulus (Alsop 2011; Pan et al. 2011). The fundamental difference between functional connectivity using BOLD and ASL is that the former essentially examines networks that comprise very slow frequency inter-regional synchronizations and the latter examines focal neuronal activity based on rCBF (Fig. 3). The newly developed pseudo-continuous ASL (pCASL) provides excellent spatial resolution, signal-to-noise ratio sensitivity, and reliability, and corresponds with ^{15}O-PET data (Dai et al. 2008; Xu et al. 2010; Wu et al. 2010).

Therefore, although BOLD fMRI can identify stimulus-evoked activity or low frequency functional connectivity, it cannot quantitatively measure ongoing activity within a focal region of the brain. Thus, in the context of chronic pain, BOLD fMRI can only detect stimulus-evoked activity (related to allodynia or hyperalgesia) or very slow inter-regional synchronization, whereas pCASL can uniquely measure brain activity in a specific focal brain area related to ongoing spontaneous pain—the most pronounced feature of most chronic pains. The first studies of pain with ASL demonstrated that the technique could reliably identify acute pain-evoked activity in brain regions previously associated

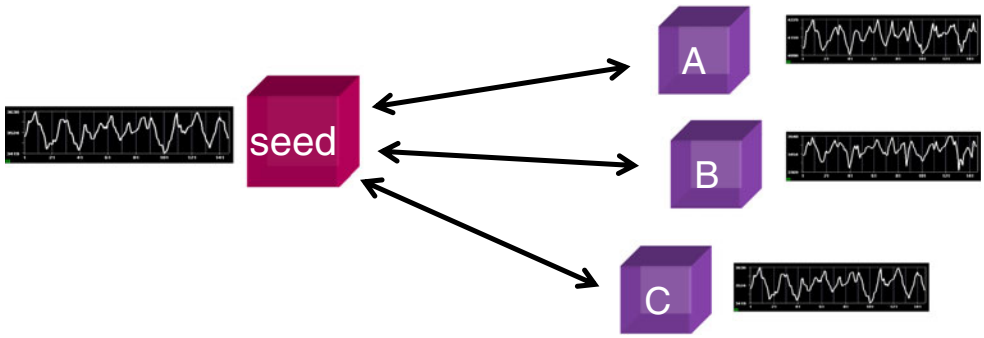

Fig. 4 Seed-based functional connectivity. The resting-state BOLD signal from a seed region of interest is extracted and used to interrogate other brain regions to locate areas of tightly correlated activity with the seed region activity

with acute pain using BOLD fMRI (Owen et al. 2008; Owen et al. 2010). However, the most exciting application of pCASL is that it provides a unique opportunity to non-invasively study regional brain activity related to spontaneous chronic pain that is not possible with other non-invasive imaging methods (i.e., PET imaging requires the use of radioisotopes) (Tracey and Johns 2010) (Fig. 3). Recent studies have also verified that ASL can detect brain activity related to post-surgical pain (Howard et al. 2011), low back pain (Wasan et al. 2011), migraine (Kato et al. 2010), and pain modulation during meditation (Zeidan et al. 2011) and future ASL-based studies can now be designed to test models of chronic pain such as the one depicted in Fig. 1.

Structural MRI: pain-related gray and white matter abnormalities

Structural MRI (sMRI) can quantify gray matter and white matter in humans (Smith et al. 2006), and so these technologies can be used to assess brain plasticity in terms of gray matter volume, cortical thickness, and to assess white matter integrity and connectivity. White matter findings have been linked to gray matter function (Behrens and Johansen-Berg 2005; Geha et al. 2008), structural connectivity has been linked with resting state functional connectivity (Greicius et al. 2004), and a relationship between anatomical connectivity and functional activity has been demonstrated (Honey et al. 2009; Smith et al. 2009; Eickhoff et al. 2010; Mars et al. 2011). Thus, both fMRI and sMRI methods are complementary to each other, providing insight into structure-function relationships associated with pain perception and antinociception (Fig. 5).

Gray matter volume and cortical thickness

Gray matter is often measured with the technique of voxel-based morphometry (VBM) (Ashburner and Friston 2000). This method can be used to locate subcortical and cortical areas of statistically significant differences in regional gray matter density (i.e., partial volume effect due to gray matter) between subject groups. A complementary method to VBM is called cortical thickness analysis (CTA) which measures scalar values of cortical thickness.

To date, only two studies have investigated structural gray matter correlates of acute pain. Teutsch and colleagues (Teutsch et al. 2008) demonstrated that 20 min of noxious stimulation over eight days in healthy subjects induced increased gray matter volume in the premotor cortex, MCC, S1, inferior parietal lobule, and the medial temporal gyrus (Teutsch et al. 2008). These changes were accompanied by functional changes: subjects habituated behaviourally (i.e., they reported the same stimulus as less painful) (Bingel et al. 2007; Teutsch et al. 2008; Bingel et al. 2008), and showed decreased pain-evoked activation in the thalamus, S2, insula and the putamen, and increased activation in the subgenual ACC (Bingel et al. 2007). Although not explicitly tested, it is inferred that these structural changes observed were related to the pain habituation. These findings provide evidence that repeated noxious stimulation induces structural brain plasticity. Additionally, a recent study in our lab (Erpelding et al. 2012b) found that cortical thickness in S1 is correlated with individual subjects' heat and cold pain sensitivity, and cortical thickness of the MCC correlated with heat pain sensitivity.

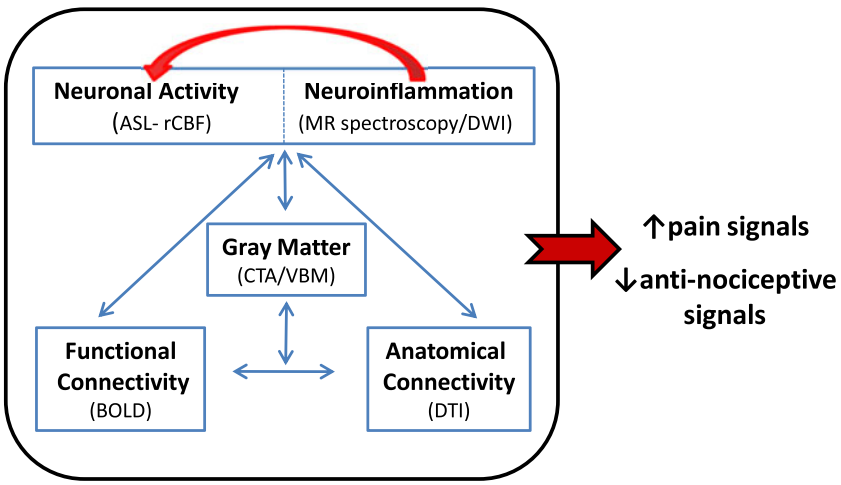

Fig. 5 A model of chronic pain whereby there are increased pain signals and decreased antinociception signals can be tested using brain imaging measures of brain anatomy, connectivity and function. Four types of MRI metrics can be used to measure brain structure and function but the structure-function relationship is not understood: 1) Neuronal activity within a focal brain area—with arterial spin labeling (ASL)—a perfusion MRI method to quantify regional cerebral blood flow (rCBF), 2) Gray matter—with cortical thickness analysis and voxel based morphology, 3) White matter connectivity between brain regions—with diffusion tensor imaging, 4) Functional connectivity between brain areas—synchronization of low frequency oscillations, with resting state BOLD fMRI

In chronic pain, the most common brain regions showing gray matter abnormalities are the PFC, insula, ACC and MCC (for a summary of all the studies that have found abnormalities in chronic pain, see Table 1). Other regions found to be abnormal in chronic pain include the thalamus, basal ganglia, S1, S2, and brainstem. Additionally, some studies have reported abnormalities in the temporal lobe and the posterior cingulate cortex. In every region, with the exception of the basal ganglia and the brainstem, most studies showed a decrease in gray matter in chronic pain. We studied two cohorts of patients with irritable bowel syndrome and found gray matter thinning in regions of the MCC and anterior insula (Davis et al. 2008; Blankstein et al. 2010), corresponding to the regions we previously reported deficits in rectal-evoked fMRI responses (Kwan et al. 2005b) and more recently found to be normally functionally connected (Taylor et al. 2009).

Interestingly, recent evidence suggests that some gray matter abnormalities in some chronic pain disorders are caused by the pain, rather than pre-existing abnormalities. For instance, we reported that thalamic gray matter volume is related to the duration of pain in patients with temporomandibular disorder (Moayedi et al. 2011). Recent evidence from longitudinal studies has provided further support for this hypothesis. For example, Rodriguez-Raecke and colleagues (Rodriguez-Raecke et al. 2009) showed gray matter abnormalities in several brain region of patients with primary hip osteoarthritis. These patients underwent surgery, which, for the most part, resolved the pain. Post-operative scans of a subgroup of these patients revealed that some, but not all, of the gray matter abnormalities had resolved (i.e., there were no differences between controls and patients). Four other studies have since demonstrated similar effects—partial reversal of brain gray matter abnormalities after patients' pain has been resolved—in the same (Gwilym et al. 2010) and other chronic pain disorders, including chronic low back pain (Seminowicz et al. 2011) and chronic post-traumatic headache (Obermann et al. 2009). However, it is unclear whether these gray matter changes occur because the chronic pain *per se* resolves or whether they are due to other secondary events. For instance, it is possible that a person with chronic pain in the hip will be more sedentary, compared to when they are no longer in pain. Furthermore, pain has been associated with changes in mood, including increased incidence of depression and anxiety, which could resolve once the pain is gone. Thus, the changes in lifestyle could feasibly alter both motor and affective brain regions. Also, it has recently been shown that medications, such as painkillers, can alter the structure of the brain (Younger et al. 2010; Walther et al. 2011). Therefore, when patients are no longer taking painkillers, brain abnormalities may resolve.

It is noteworthy that not all of the observed gray matter abnormalities were abolished with the cessation of pain. This may be related to lasting effects of medications, such as opiates, which have been shown to produce long-term changes in the cingulate cortex, amygdala, PFC, hypothalamus, brainstem, and the hippocampus of patients with chronic low-back pain (Younger et al. 2010). These changes did not show reversal after the patients had ceased managing their pain with morphine for many months. It is also noteworthy that functional pain syndromes, such as irritable bowel syndrome, fibromyalgia, and temporomandibular disorder, are defined as disorders that disturb normal function without any obvious structural or biochemical abnormality (Diamant 1995). Therefore, it is possible that mechanisms other than increased nociceptive drive from the periphery may be driving gray matter abnormalities in the brain. An alternative possibility is that gray matter abnormalities predate the onset of chronic pain. In this scenario, gray matter abnormalities are pre-existing vulnerabilities that may contribute to the development of chronic pain (Davis 2011). Evidence for this proposition comes from studies that have identified regions of gray matter abnormalities related to stable personality traits, such as neuroticism or pain catastrophizing (Schweinhardt et al. 2008; Blankstein et al. 2010) which are related to heightened pain sensitivity. We have recently demonstrated that pain helplessness, a subscale of the Pain Catastrophizing Scale (Sullivan et al. 1995) is related to gray and white matter structure in temporomandibular disorder patients.

In sum, there are both pre-existing and pain-driven gray matter abnormalities in the brain of chronic pain patients. In general, there appears to be increases in sensory/nociceptive brain regions, indicative of increased nociceptive drive; decreases in pain modulation brain regions, indicative of potentially dysfunctional pain-modulatory systems.

The pathophysiology of pain-related gray matter abnormalities is not understood. However, insight may be gained by examining MRI-detectable changes that occur as part of the natural aging process, with increased use (experience, learning and memory), as well as in response to injuries including deafferentation and amputation. Pakkenberg and Gundersen (1997) reported that whole brain age-related atrophy in humans is due to neuronal loss and reduced cell packing density. However, Peters et al. (Peters et al. 1998) reported that age-related atrophy in macaques is not related to a decrease in the number of neurons but could be due to changes in other gray matter constituents (e.g., glia) or biochemical changes within cells. There are also other proposed hypotheses to explain mechanisms of gray matter change: for instance, rather than neural loss, there may be glial death (May 2008). Recent evidence suggests that gray matter loss may be related to the density of small dendritic spines (Metz et al. 2009; Dumitriu et al. 2010), and the remodeling of neuronal processes (Lerch et al. 2011). Alternatively, reversible gray matter changes in chronic pain may

Table 1 Gray matter abnormalities in chronic pain populations

Chronic pain disorder	Reference	Thal	BG	S1	S2	IC	ACC	MCC	M1	PFC	Brainstem	Other
CBP	Apkarian et al., 2004	↓								↓ dlPFC		
	Schmidt-Wilcke et al., 2006	↑	↑ putamen	↓						↓ dlPFC		↓ pTL, TL
	Buckalew et al., 2008											↓ PPC
	Seminowicz et al., 2011			↓		↓	↓			↓ vlPFC, dlPFC, OFC		↑ MTL
FMS	Kuchinad et al., 2007					↓		↓		↓ mPFC		↓ PCC, PHG
	Schmidt-Wilcke et al., 2007	↓	↑							↑ OFC		↓ STG,↑ Cereb
	Lutz et al., 2008											↓ HC
	Wood et al., 2009							↓				↓ PHG, PCC
	Burgmer et al., 2009 Puri et al., 2010						↓			↓ vlPFC		↓ Amyg ↓ SMA
	Robinson et al., 2011					↓		↓				↓ PCC
IBS	Davis et al., 2008	↓				↓	↓	↓				
	Blankstein et al., 2010							↓				↑ HT
	Seminowicz et al., 2010	↓	↓ vStr, Put		↑	↑	↑			↑ OFC, dlPFC;↓ vlPFC, FP, mPFC		↑ HC

Chronic pain disorder	Reference	Thal	BG	S1	S2	IC	ACC	MCC	M1	PFC	Brainstem	Other
Migraine	Rocca et al., 2006						↓			↓ dlPFC, vlPFC	↑ PAG	↓ TL
	Schmidt-Wilcke et al., 2007					↓	↓	↓				
					↓					↓ vlPFC		↓ TL
	Valfrè et al., 2008*				↓	↓		↓		↓ vlPFC, dlPFC		↓ Amyg
	DaSilva et al., 2007			↑								
				↑					↑			
	Kim et al., 2008					↓		↓	↓	↓ dmPFC, dlPFC, OFC		↓ PPC, PMC, V1
TNP	DaSilva et al., 2008			↑/↓		↑/↓	↓	↑	↑/↓	↓ Frontal pole, vlPFC, dlPFC		↓PCC
TN	Gustin et al., 2011	↓	↓ vStr, Put	↓		↑/↓						
TMD	Younger et al., 2010	↑	↑ GP, Put	↓		↑				↑ vlPFC	↑	
	Moayedi et al., 2011			↑						↑ vlPFC, Frontal pole		
	Gerstner et al., 2011					↓		↓		↓ vlPFC		↓ PCC, TL, PHG
Phantom-limb	Draganski et al., 2006	↓VPL										
PVD	Schweinhardt et al., 2008		↑ GP, SN, NC									↓ HC, PHG
CRPS	Geha et al., 2008		↓ NAcc			↓	↓			↓ vmPFC		
CH	May et al., 1999											↑ HT

be caused by neuroinflammation (Watkins et al. 1995; DeLeo et al. 2004; Guo and Schluesener 2007) and induce MRI-detectable increases in gray matter. For the observed gray matter losses, however, we cannot rule out cell death as a factor in age-related gray matter loss—healthy populations lose neurons as they age, and persons with neurodegenerative diseases suffer increased rates of atrophy related to cell death.

White matter integrity and putative markers of neuroinflammation

Diffusion tensor imaging (DTI) is an MRI acquisition that is sensitive to the diffusion of water molecules (Mori and Zhang 2006). This technique allows us to visualize white matter tracts (Behrens et al. 2003a) because in the nervous system the dominant direction of water diffusion is along the long axis of axons. There are several DTI measures that provide information about white matter: fractional anisotropy (FA) is most often used to a reflection of white matter integrity (Basser and Pierpaoli 1996; Moseley et al. 2002). FA is scaled between 0 and 1, where 0 represents completely unrestricted diffusion, and 1 represents complete anisotropic diffusion. Other metrics such as mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (λ_1), reflect different aspects of white matter microstructure. There could be macrostructural factors that contribute to reduced FA, such as increased branching, crossing fibres or larger tracts (more axons) and/or microstructural changes such as cell swelling (edema), changes to protein filaments (neurofilament phosphorylation), disruptions to the cell membranes, and, to a certain extent, decreased myelin (Beaulieu 2002; Beaulieu 2009). However, as FA is a summary measure, it is not specific to any microstructural features of white matter tracts (Pierpaoli et al. 1996). Histological studies have demonstrated that RD and λ_1 are related to alterations in specific structures . FA can be increased by any decrease in RD, and increases in λ_1, and thus RD and λ_1 provide greater insight into the cellular properties underlying the observed changes in FA, and presumably, white matter tracts. Specifically, RD is related to membrane integrity, and,

Table 1 (Continued)

Chronic pain disorder	Reference	Thal	BG	S1	S2	IC	ACC	MCC	M1	PFC	Brainstem	Other
CTTH	Schmidt-Wilcke et al., 2005					↓	↓	↓		↓ OFC	↓	↓ PCC, PHG, pTL, Cereb
MOH										↓ OFC	↓	
HypH	Holle et al., 2011				↓					↓ dlPFC		↓ HT, PCC, TL, Cereb
CPP	Farmer et al., 2011**											
CPTH	Obermann et al., 2009***							↓		↓ dlPFC		
	Obermann et al., 2009‡	↑									↑	
PIFP	SchmidtWilcke et al., 2010			↓		↓	↓		↓	↓ dlPFC, vmPFC		
Hip OA	RodriguezRacke et al., 2009			↓	↓	↓	↓			↓ vmPFC, OFC, vlPFC,↑/↓ dlPFC[r]	↓	↓ Cereb, Amyg
	Rodriguez-Racke et al., 2009‡‡				↑	↑	↑			↑ dlPFC	↑	↑ Amyg
Rheum Arth	Wartolowska et al, 2012		↑ Put, NAcc, NC									
Pain disorder[a]	Valet et al., 2009					↓		↓		↓ vmPFC, OFC		↓ iTL, PHG

Amyg amygdala, *ACC* anterior cingulate cortex, *BG* basal ganglia, *Cb* cerebellum, *CH* cluster headache, *CPP* chronic pelvic pain, *CPTH* chronic posttraumatic headache, *CRPS* complex regional pain syndrome, *dlPFC* dorsolateral prefrontal cortex, *dmPFC* dorsomedial prefrontal cortex, *GP* globus pallidus, *HC* hippocampus, *Hip OA* hip osteoarthritis, *HT* hypothalamus, *HypH* hypnic headache, *IBS* irritable bowel syndrome, *IC* insular cortex, *iTL*-inferior temporal lobe, *M1* primary motor cortex, *MCC* midcingulate cortex, *MOH* medication-overuse headache, *mPFC* medial prefrontal cortex, *MTL* medial temporal lobe, *NC* caudate nucleus, *OFC* orbitofrontal cortex, *PCC* posterior cingulate cortex, *PFC* prefrontal cortex, *PHG* parahippocampal gyrus, *PIFP* persistent idiopathic facial pain, *PMC* premotor cortex, *PPC* posterior parietal cortex, *pTL* posterior temporal lobe, *Put* putamen, *PVD* provoked vestibulodynia, *Rheum Arth* rheumatoid arthritis, *S1* primary somatosensory cortex, *S2* secondary somatosensory cortex, *SMA* supplementary motor area, *SN* substantia nigra, *STG* superior temporal gyrus, *Thal* thalamus, *TMD* temporomandibular disorder, *TN* trigeminal neuralgia, *TNP* trigeminal neuropathic pain, *TL* temporal lobe, *V1* primary visual cortex, *vlPFC* ventrolateral prefrontal cortex, *vmPFC* ventromedial prefrontal cortex, *vSTR* ventral striatum

[a] Pain disorder is a diagnosis based on the DSM-IV, defined as persistent and chronic pain at one or more sites that cannot be fully explained by a physiological process or physical disorder.

*Between patient groups analysis: Chronic vs. Episodic

**This study did not identify group differences, but did identify correlations between gray matter and pain characteristics

***This study did not identify group differences—the reported differences are from comparing temporary post-traumatic headache to chronic post-traumatic headache (temporary>chronic)

‡This study did not identify group differences—the reported differences are from a longitudinal study comparing time 1 scans with subjects after the pain has resolved

‡‡Longitudinal study comparing time 1 scans with post-operative scans, when pain is resolved

to some extent, myelination; whereas λ_1 is related to factors that may disrupt the axon or neurofilament phosphorylation.

Recent studies have suggested that chronic pain may induce neuroinflammation in the brain (Watkins et al. 1995; DeLeo et al. 2004; Guo and Schluesener 2007), which can lead to changes in both gray matter and white matter that can be detected by MRI. Therefore, changes in the measures of white matter microstructure may, in fact, be related to neuroinflammation rather than increases or decreases in the number or size of cells and/or axons present in the fields being studied. In this scenario, we would expect that changes in FA are associated to changes in MD and RD, which are markers of inflammation and/or edema (Basser and Pierpaoli 1996; Beaulieu 2002). The first study to test for abnormalities in white matter microstructure associated with chronic pain, by DaSilva and colleagues (DaSilva et al. 2007), reported decreased FA along tracts between the brainstem and the thalamus and the thalamus and S1 cortex of patients with migraine. The authors concluded that there are abnormalities along the ascending nociceptive pathways in migraine patients.

Geha and colleagues (Geha et al. 2008) reported white matter abnormalities in patients with complex regional pain syndrome that consisted of lower FA in the cingulum bundle and the adjacent corpus callosum. This was the first study to investigate the abnormalities in white matter tracts by elucidating the connectivity of the region. They reported that abnormal white matter region had fewer connections per unit of distance in CRPS patients compared to controls.

Our lab has investigated white matter abnormalities in patients with irritable bowel syndrome (Chen et al. 2011) and in temporomandibular disorder (Moayedi et al. 2012). In irritable bowel disorder, we found that the patients had increased FA in the fornix and the external/extreme capsule, adjacent to the insula. We also found that FA in the anterior insula and the ventroposterior lateral (VPL) thalamus correlated with pain severity. Further, FA in the left insula correlated with pain unpleasantness and duration. Finally, we found that FA in the cingulum bundle was negatively correlated to pain catastrophizing scores, and that there was a positive correlation between FA in the medial thalamus and neuroticism. These findings suggest that patients with

irritable bowel disorder have abnormal connections in white matter tracts related to nociception and/or cognitive/limbic function. In temporomandibular disorder, we found widespread reduced FA and increased MD and RD in white matter tracts. In particular these abnormalities were located in the microstructure of the corpus callosum, the internal and external capsule, and white matter tracts associated with the thalamus and primary sensorimotor cortex.

Another study by Szabo and colleagues (Szabo et al. 2012) identified white matter abnormalities in a region where several prominent white matter tracts intersect in patients with migraine. Because of the complexity of the region of white matter, they used probabilistic tractography (see below) to characterize differences in FA. They found that the region was less connected to several pain related regions, including the brainstem; however, these observations were only qualitative.

In addition to the aforementioned studies that have investigated white matter abnormalities in the brains of chronic pain patients, three DTI studies have investigated abnormalities along the trigeminal nerve in patients with trigeminal neuralgia or temporomandibular disorder. One study of trigeminal neuralgia (Fujiwara et al. 2011) did not find any significant abnormalities in the FA, MD, or the cross-sectional area of the patients' trigeminal nerve. This study reported that no significant group differences in the ratio of FA of the affected to the unaffected nerve. However, the study reported significantly more variance in the FA values of patients' trigeminal nerves, compared to controls, and this value was positively correlated to the affected:unaffected ratio of the cross-sectional area of the trigeminal nerve. In another study of trigeminal neuralgia, Leal et al. (2011), reported that the affected trigeminal nerve had significantly increased MD, and decreased FA, nerve volume, and cross-sectional area. Furthermore, the decrease in FA was positively correlated to the decrease in volume and cross-sectional area of the trigeminal nerve. Decreased FA and increased MD indicate that there is increased diffusion, or less organization. Therefore, it is possible that the trigeminal nerve has a larger diameter, is inflamed, or is damaged. However, the interpretation is limited as other measures of white matter integrity (RD and λ_1) were not provided. Our recent study supports the concept that an inflamed trigeminal nerve contributes to chronic pain in temporomandibular disorder since we found that patients had lower FA that was negatively correlated to pain durations, and increased MD and RD in their trigeminal nerves (Moayedi et al. 2012). These studies indicate that there are structural abnormalities along the trigeminal nerves in patients with trigeminal chronic pains. One key question to be investigated in the future is whether inflammatory processes that occur during pain induce these peripheral nerve abnormalities, or whether there is increased or ectopic neural activity that causes the abnormalities over time.

White matter connectivity between brain areas (diffusion tensor imaging/tractography)

The trajectory of white matter tracts can be assessed with various tractography methods. One approach, probabilistic tractography, can delineate pathways between a seed area and target areas, and can calculate the probability of connection between these regions (Behrens et al. 2003b; Behrens et al. 2007; Kucyi et al. 2012). Thus, white matter connectivity fingerprints can be constructed complementary to the functional connectivity fingerprints described above. The sensitivity and specificity of current tractography methods can be excellent (>80 %) as validated in human and animal histology studies (Dyrby et al. 2007; Seehaus et al. 2012). However, tractography using conventional 3 T MRI scanners is limited by millimeter voxel resolution and the problem in resolving multiple fiber orientations and crossing fibers that occur within single voxels (Le and Johansen-Berg 2012).

In addition to delineating tracts in healthy populations, we have used tractography to reveal pathways related to maladaptive pain-related helplessness in temporomandibular disorder (Salomons et al. 2012). This study revealed tracts connecting the SMA, MCC and descending to the corticospinal tracts are related to helplessness. We also recently reported that patients with temporomandibular disorder had reduced white matter connectivity between the genu of the corpus callosum and the dorsolateral PFC, and increased connectivity between the corpus callosum and the frontal pole (Moayedi et al. 2012). These abnormalities may be related to dysfunctional antinociceptive pathways in temporomandibular disorder and the cognitive load of pain.

Pain-attention interactions

It is well known that there exists an interaction between pain and attention such that in some instances, pain interferes with attention and cognitive processing, while in other situations engagement in a cognitive task can attenuate the pain experience (Eccleston 1995; Legrain et al. 2009). The magnitude of pain attenuation in experimental pain settings may vary from mild to modest based on conditions (Seminowicz and Davis 2007a), but the outcome of this interaction has profound impact on the effect of chronic pain on cognitive function on one hand (Kewman et al. 1991; Eccleston et al. 1997; Park et al. 2001; Dick et al. 2002), and the potential for chronic pain control through cognitive coping strategies on the other hand (Pincus and Morley 2001).

We have explored the brain mechanisms underlying acute and chronic pain-cognition interactions. We found that healthy individuals exhibit one of two types of behavioural outcomes from competing acute pain and cognition resources

(Seminowicz et al. 2004). In this study, subjects were required to perform an attention-demanding cognitive task, the Stroop task, in the presence or absence of concurrently applied acute pain stimuli. As we anticipated, one group of subjects, deemed the P-group for pain dominates, the presence of pain impaired the subjects' ability to perform the Stroop (i.e., task reaction time (RT) increased during concurrent pain). However, we also unexpectedly found that in the other group of subjects, deemed the A-group for attention dominates, subjects actually improved their task performance (i.e., RTs decreased) during concurrent pain. Interestingly, we then found that in the A-group, but not the P-group, cognitive engagement in the Stroop task attenuated pain-evoked fMRI responses in S1, S2 and the anterior insula—key brain areas of the pain system. Interestingly though, the initial early pain-evoked responses were greater for the A-group than the P-group, perhaps indicative of greater salience detection that could more effectively engage the descending pain modulation system. These findings highlight individual differences in coping mechanisms and raise the possibility that a specific type of individual may be better able to cope with chronic pain through their inherent biology or that they may be more amenable to cognitive coping strategies learned through approaches such as cognitive behaviour therapy. The structural underpinnings of these two types of behavioural phenotypes are not yet fully understood but our preliminary studies indicate that P-type individuals have increased gray matter in the insula, mid cingulate cortex, supplementary motor cortex, orbitofrontal cortex, thalamus and caudate nucleus compared to A-type individuals (Erpelding et al. 2010; Erpelding et al. 2012a).

We also studied how patients with chronic temporomandibular pain respond to Stroop tasks, including variants with an emotions component related to temporomandibular pain (Weissman-Fogel et al. 2011). We found that the patients had slower reaction times than the healthy controls, akin to the P-type classification. Interestingly, the patients reported that most of the words presented in the Stroop task strongly affected their emotion whereas most of the Stroop words did not have any emotional effect in the health controls. We also found increased Stroop task-evoked fMRI responses (compared to controls) in cortical areas associated with cognitive and emotion functions (e.g., PFC, amygdala, perigenual cingulate) and decoupling of the normally coupled prefrontal-cingulate and amygdala-cingulate fMRI correlated activities. These findings suggest that the chronic pain patients show a heighted emotional response when trying to balance their chronic pain with cognitively and emotionally challenging tasks.

Individual factors impact pain

Adaptation to ongoing noxious stimuli can be an advantage in chronic pain, but habituation or summation to sustained/repeated painful stimuli can vary (Price et al. 1980; Price et al. 1989; Vierck et al. 1997; Hashmi and Davis 2008; Hashmi and Davis 2009) and some people experience less pain when engaged in a cognitive task. Males and females also can have different pain experiences. For example, we found that women demonstrated greater adaptation to prolonged experimental heat pain stimuli and greater habituation to repeated heat pain stimuli compared to men (Hashmi and Davis 2009).

There are many personality factors that can impact the pain experience and individual brain responses to pain. For example, pain catastrophizing, an "exaggerated negative mental set brought to bear during actual or anticipated pain experience" (Keefe et al. 1989; Sullivan et al. 2001; Turk 2002), comprises rumination, magnification, and helplessness (Osman et al. 1997; Osman et al. 2000; Sullivan et al. 2001), and can be assessed with the Pain Catastrophizing Scale (Sullivan et al. 1995). Pain catastrophizing has been linked experimentally to increased pain sensitivity and pain as well as chronic pain (Severeijns et al. 2001; Sullivan et al. 2001; Seminowicz and Davis 2006; Edwards et al. 2006; Taylor et al. 2010). Individuals with high pain catastrophizing scores do not cope with pain well and may be predisposed to develop chronic pain (Pavlin et al. 2005; Forsythe et al. 2008; Papaioannou et al. 2009; Sullivan et al. 2009). This may arise in part from an inadequate descending pain modulation system. We found that pain-evoked brain activity in the insula and ACC strongly correlate with PCS scores (Seminowicz and Davis 2006). Furthermore, evoked activity in the dorslolateral PFC of the descending modulation system negatively correlated with PCS scores. We also found correlation of PCS in chronic pain was strongly correlated to dorsolateral PFC gray matter thinning and decreased white matter in the cingulum (Blankstein et al. 2010; Chen et al. 2011). Furthermore, we found patients with temporomandibular disorder had an abnormal relationship between helplessness and MCC gray matter, mediated by the corticospinal tract (Salomons et al. 2012). In these patients there was also a positive correlation between neuroticism and gray matter thickness of the orbitofrontal cortex that is not seen in healthy controls (Moayedi et al. 2011). There are many other studies beyond the scope of this review that highlight the contribution of individual characteristics in pain related behaviours, and brain structure and function.

Clinical relevance of pain imaging and personalized medicine

Chronic pain control is partly hampered by a lack of therapeutic targets that produce analgesic effects with minimal side effects. However, in the future, functional and structural

neuroimaging may serve as a useful adjunct for clinical assessment and treatment of chronic pains. For example, as summarized in this article, neuroimaging has shown that the brain not only undergoes plasticity associated with chronic pain but also has the capacity to normalize after effective therapies. Therefore, knowledge gained from fundamental neuroimaging studies of pain may provide insight into biomarkers of chronic pain and the optimal time to intervene with treatment and also can provide insight into potential side effects of treatment (e.g., based on connectivity studies). Importantly, the intersubject variability in both function and structure revealed through neuroimaging can be used to tailor treatment (i.e., personalized medicine). Personalized targeting of key regions of the brain's nociceptive or modulation system while avoiding other areas that control important sensory or cognitive functions (directly or indirectly) could minimize serious side effects of treatment while maximizing analgesia. Thus, more effective treatment of pain might then be based on individual complexities of brain structure and function, rather than a "one size fits all" approach.

However, a great deal of development is still needed before neuroimaging can be applied to individual patients for clinical purposes. For example, although normative group findings in pain imaging studies are relatively consistent, there is individual variability in pain responses across the normal population. Therefore diagnostics of a single individual's finding would need to be evaluated against findings from a very large and diverse normative group. It is critical to address these issues to avoid false negative or false positive findings. There are also significant neuroethical issues related to neuroimaging findings that should be addressed to protect individual privacy, and to ensure that there are no untoward employment, health insurance, and mental health outcomes of inadequate neuroimaging-based diagnostics (for a full discussion, see (Davis 2003; Davis 2006; Davis et al. 2012)).

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