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Cortical changes in chronic low back pain: Current state of the art and implications for clinical practice

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ABSTRACT

There is increasing evidence that chronic pain problems are characterised by alterations in brain structure and function. Chronic back pain is no exception. There is a growing sentiment, with accompanying theory, that these brain changes contribute to chronic back pain, although empirical support is lacking. This paper reviews the structural and functional changes of the brain that have been observed in people with chronic back pain. We cast light on the clinical implications of these changes and the possibilities for new treatments but we also advise caution against concluding their efficacy in the absence of solid evidence to this effect.

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1. Introduction

Chronic musculoskeletal pain is almost by definition a problem for which previous treatment has been unsuccessful. The clinical stories of patients with problems such as chronic low back pain (CLBP), fibromyalgia, and late whiplash associated disorder are usually ones of confusing and conflicting diagnoses and multiple treatment failures. Diagnosis and treatment has traditionally focused on what Robinson and Apkarian (2009) have called 'end organ dysfunction'. That is, clinicians and researchers have looked to structural and functional abnormalities within the musculoskeletal system for a driver of the clinical condition and treatment has sought to normalise peripheral pathology and mechanics (stretch it, splint it, remove it, anaesthetise or denervate it). In general terms the 'end organ dysfunction' approach might be considered to have proven unsuccessful for these conditions (see for e.g. van Tulder et al., 2006a; van Tulder et al., 2006b). Neuroimaging studies have revealed numerous structural and functional changes within the brains of people with chronic musculoskeletal pain and there is growing opinion that these changes may contribute to the development and maintenance of the chronic

pain state (Apkarian et al., 2009; Tracey and Bushnell, 2009). In this model of chronic pain the brain is seen as an explicit target for treatment and several treatment strategies have been developed and modified to fit this aim. Although there are data available on a range of chronic painful disorders, we will focus here on the cortical changes observed in patients with CLBP and the possible clinical implications for this population.

2. Brain changes in people with CLBP

Advances in neuroimaging technology have led to rapid increases in our understanding of the human brain in health and disease. Methodologies such as functional magnetic resonance imaging, voxel-based morphometry, magnetic resonance spectroscopy, magnetoencephalography and electroencephalography (EEG) give us insight into multiple dimensions of the brain state. Changes can be broadly categorised as neurochemical, structural or functional.

2.1. Neurochemical changes

Several studies have compared the neurochemical profile of healthy controls with those of CLBP patients. Significant changes (some markers increase, others decrease) in the neurochemical profile in the dorsolateral prefrontal cortex (DLPFC), thalamus and

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orbitofrontal cortex have been observed in people with CLBP and, by and large, the magnitude of the shift from normative data increases as the duration and intensity of pain increase (Grachev et al., 2000). Further, co-morbid anxiety (Grachev et al., 2001; Grachev et al., 2002) and depression (Grachev et al., 2003) seem to be associated with larger effects. Magnetic spectroscopy data suggest that the magnitude of shifts in neurochemical profile in anterior cingulate cortex, thalamus and prefrontal cortex can differentiate between those with CLBP and healthy controls (Siddall et al., 2006). Similar changes have been reported from studies involving people with neurodegenerative conditions such as Alzheimer's disease and multiple sclerosis, which has led to the proposal of a relationship between chronic pain and neuronal loss and degeneration (Grachev et al., 2000). Notably, although there is clear evidence that brain neurochemistry is awry in people with CLBP, there is no evidence to suggest that neurochemical changes cause CLBP. In fact, there is reasonable argument that CLBP may cause neurochemical changes – certainly the neuroanatomical distribution of the changes is consistent with the established 'pain matrix' and exaggerated and ongoing neural activity can lead to shifts in neurochemistry consistent with those observed. However, the possibility that these changes are at once a result and cause of ongoing pain remains. Clearly, longitudinal data are required.

2.2. Structural changes

Brain structure can be compared between people with CLBP and controls via voxel-based morphometry. In short, voxel-based morphometry is a statistical method of comparing the volume of gray and white matter in specific brain areas, that controls to a large extent for the variable shape of human brains by normalising data to anatomical landmarks (Schmidt-Wilcke, 2008). Voxel-based morphometry is not without problems – its assumptions are yet to be fully tested – but it has provided fairly compelling evidence of reduced gray matter in the DLPFC (Apkarian et al., 2004b; Schmidt-Wilcke et al., 2006), the right anterior thalamus (Apkarian et al., 2004b), the brainstem, the somatosensory cortex (Schmidt-Wilcke et al., 2006) and the posterior parietal cortex (Buckalew et al., 2008) of people with CLBP. Apkarian et al. (2004b) found that a combination of sensory and affective dimensions of pain strongly predicted DLPFC gray matter changes and Schmidt-Wilcke et al. (2006) demonstrated strong correlations between the extent of density changes and pain intensity and unpleasantness. It is worthwhile contemplating what these extraordinary findings actually mean – there seem to be fewer brain cells in these areas, or at least less neuron-matter, in people with CLBP than there is in healthy controls. Because it relates to the matter by which we exist, these discoveries appear remarkable, but are they as catastrophic as they seem? Probably not – gray matter increases with training in the injured brain (Gauthier et al., 2008) and it seems reasonable to suggest that at least the same response might occur in the uninjured brain.

2.3. Functional changes

2.3.1. Cortical representation

In order to understand the notion of 'cortical reorganisation', it is helpful to first understand the notion of cortical representations. A representation can be thought of as a network of neurons that represent something else, for example a word, thought, joint, immune response, or article of knowledge. The physical body is represented in the human brain by neurons in many areas, most famously the primary somatosensory cortex (S1). S1 representation refers to the pattern of activity that is

evoked when a particular body part is stimulated. S1 representation of the back is different in people with CLBP from people without CLBP: Flor et al. (1997a) showed that the representation of the lower back in the primary somatosensory cortex (S1) is shifted medially and expanded, invading the area where the leg is normally represented and that the extent of expansion is closely associated with pain chronicity. Lloyd et al. (2008) demonstrated similar findings in CLBP patients who were distressed but not in those who were not, which raises the possibility that S1 shifts may not be a feature of CLBP so much as the emotional impact of CLBP.

2.3.2. Cortical activity and responsiveness

A number of investigations suggest that CLBP is characterised by altered cortical responses to noxious stimulation, although, again, disagreement abounds (Derbyshire et al., 2002; Baliki et al., 2006). Enhanced cortical responses have been noted with noxious subcutaneous stimulation of the back (Flor et al., 1997a) and acute experimental muscle pain (Diers et al., 2007) as well as activation of a more expansive network of pain-related brain regions with peripheral noxious input (Giesecke et al., 2004, 2006; Kobayashi et al., 2009). In addition, it appears that CLBP patients have significantly lower increases in blood flow in the periaqueductal gray (an important part of the descending antinociception system) than controls when exposed to equally painful stimuli (Giesecke et al., 2006).

Alterations in brain activity do not appear to be isolated to pain processing. Flor et al. (1997a) also noted an enhanced cortical response to *non-painful* stimulation of the back. Moreover, when exposed to non-painful vibratory stimuli, distressed CLBP patients do not show the increase in DLPFC and anterior cingulate cortex activity seen in non-distressed CLBP patients (Lloyd et al., 2008), a finding that suggests different descending modulatory control in the presence of distress. CLBP patients show a selectively enhanced EEG signal to pain-related words, while no difference is seen for body-related or neutral words which the authors suggest indicates altered implicit pain memories (Flor et al., 1997b). Differences in the 'resting' brain have also been reported – medial prefrontal cortex seems to remain active during task performance in people with CLBP whereas it 'deactivates' in healthy controls (Baliki et al., 2008). Although preliminary, such a finding raises the possibility that brain activity is different in people with CLBP from those without, even when the brain is not involved in processing noxious input.

Shifts in primary motor cortex representation have also been reported in people with CLBP. M1 is organised according to movements, not muscles (Wolpert et al., 2001). Tsao et al. (2008) found that the motor cortical representation of contraction of the transversus abdominus muscle was shifted and enlarged in patients with recurrent LBP and that both the location and size of the map volume were associated with slower onset of transversus abdominus as part of the postural adjustment associated with rapid arm movement. People with CLBP also exhibit an expanded area of cortical activity in preparation for arm movement and a decrease in specific cortical responses in relation to observed delayed onset of deep abdominal muscles (Jacobs et al., 2010). Furthermore, raised motor thresholds have been reported for the lumbar back muscles of CLBP patients (Strutton et al., 2005), which suggest decreased corticospinal drive to these muscles. Clearly, the picture is expanding, but it is not immediately obvious, how these findings should best be interpreted – whether or not delayed activation of Transversus Abdominis during rapid limb movements contributes to CLBP has not been settled, although a link in the opposite direction seems probable (Moseley et al., 2004; Moseley and Hodges, 2005; Moseley and Hodges, 2006).

3. Clinical implications of brain changes

The clinical implications of an altered brain state on the chronic pain experience are far from being fully understood (Apkarian et al., 2009). However, it is already possible to make three observations that are of particular importance to therapists managing patients with CLBP.

3.1. Enhanced/increased response to noxious stimuli

The neurochemical and functional changes that have been observed in people with CLBP should sensitise the neural networks that subservise nociception and pain. That is, brain areas that demonstrate neurodegeneration are known to be involved in antinociception, as are those that demonstrate reduced activation during noxious stimuli and spontaneous pain is associated with abnormalities of cortical connectivity that may cause pronociceptive activation in a kind of self-sustaining mechanism (see May 2008).

Placebo research suggests that the DLPFC has a key role in expectancy-induced analgesia. In a study of placebo analgesia Wager et al. (2004) found that during the anticipation of pain, DLPFC activity was enhanced in subjects who subsequently reported reduced pain ratings and vice versa. The level of endogenous opioid activity in the DLPFC has been shown to be associated with the size of the analgesic effect that subjects anticipated prior to the administration of a placebo (Zubieta et al., 2005) and using low frequency transcranial magnetic stimulation to temporarily disrupt DLPFC activation, Krummenacher et al. (2010) found that DLPFC inhibition did not affect experimental pain tolerance or thresholds, yet it completely blocked placebo analgesia. These data raise the possibility that decreased efficacy of the DLPFC, which is characteristic of CLBP, might increase pain. Indeed, there are behavioural data that seem consistent with this idea.

CLBP patients exhibit lower mechanical pain thresholds than healthy controls not just over the lumbar spine (Giesbrecht and Battie, 2005; Kobayashi et al., 2009), but also on the thumb nail (Giesecke et al., 2004) and a combination of sites remote to the lumbar spine (Giesbrecht and Battie, 2005); hot noxious stimulation of the hand hurts people with CLBP more than it hurts healthy controls (Kleinbohl et al., 1999); CLBP patients report more intense, more widespread and longer duration of pain after hypertonic saline injection into a shoulder muscle (O'Neill et al., 2007). Such changes in sensitivity away from the back implicate cortical rather than peripheral or spinal mechanisms. Hyperalgesia at remote sites has been shown to be positively correlated with self reported pain intensity, physical function and pain duration (Clauw et al., 1999; Ole Kudsk et al., 2009) but negatively correlated with degenerative lumbar disc disease or radiculopathy. As such, diffuse tenderness is considered to reflect disturbed nociceptive regulation rather than spinal pathology (Ole Kudsk et al., 2009). Curiously, changes in sensitivity in CLBP may not be limited to somatosensory stimuli. Small and Apkarian (2006) noted that CLBP patients rated sour taste stimuli as significantly more intense than normal controls and there is some suggestion that depressed CLBP patients have decreased habituation to repetitive auditory stimulus (Fann et al., 2005), which suggests a widespread dysfunction of normal cortical inhibitory mechanisms.

It is likely that part of the pain experience of CLBP patients is mediated by sensitivity changes within the central nervous system and the demonstrated brain changes are a probable contribution to this. This is important, particularly when one considers that a number of manual therapies are thought to mediate their analgesic effects via descending antinociception (Vicenzino and Wright, 2002) – perhaps the failure of manual therapies to significantly

influence CLBP (van Tulder et al., 2006a) is due, at least in part, to the breakdown of these antinociceptive systems in people with CLBP.

3.2. Psychological and cognitive effects

One might predict that brain dysfunction will have deleterious effects beyond the processing of noxious stimuli. Indeed, there is evidence to this effect: Apkarian et al. (2004a) found CLBP patients to be impaired on a task designed to assess emotional decision making. Performance was negatively related to pain intensity. Others have noted significant impairments in memory, language skills and mental flexibility (Weiner et al., 2006; Lourenco Jorge et al., 2009) and reduced ability to shift attention away from pictures of physical activities associated with the threat of back injury (Roelofs et al., 2005). Furthermore, whereas distraction increases pain tolerance and threshold in healthy controls, it does little in those with CLBP (Johnson and Petrie, 1997).

Whilst the psychological manifestations of CLBP are undoubtedly multifaceted and likely to be influenced by a variety of inputs, brain changes may need to be considered as an additional contributor to psychological dysfunction. Furthermore resultant deficits in cognitive function, changes in decision making and appraisal and possible modification in the relationship between expectation and pain experience may serve as added hurdles to the success of psychologically based treatments.

3.3. Altered body perception

One might also predict that disruption of cortical representations of the body will disrupt body perception. Certainly, CLBP patients exhibit deficits in proprioception (Gill and Callaghan, 1998; Taimela et al., 1999; Brumagne et al., 2000; O'Sullivan et al., 2003), perform poorly on a task that required subjects to make judgements on the direction of trunk rotation adopted by a model (Bray and Moseley, *in press*), have poorer tactile acuity (Luomajoki and Moseley, *in press*; Moseley, 2008; Wand et al., *in press*), are worse at identifying letters that are traced on their back (Wand et al., *in press*) and find it difficult to delineate the outline of their back when asked to complete a drawing of 'how it feels' (Moseley, 2008). In some cases patients report that they no longer consider their back as being a part of them and do not feel that the back can be controlled automatically (Osborn and Smith, 2006). It is also possible that the varied alterations in trunk muscle recruitment patterns evident in CLBP patients (Hodges and Moseley, 2003) may be a manifestation of a disturbance in body perception. While it is beyond the scope of this article to review the extensive literature in this area, the interdependence of body perception and movement repertoire is so tight that it persists even when amputees learn to perform normally impossible movements of their phantom arm (Moseley and Brugger, 2009), and it is not unreasonable to consider that movement abnormalities observed in people with CLBP may be a manifestation of a disruption of the working body schema, a proposition supported by the close association between lumbar tactile acuity and performance on motor control tests (Luomajoki and Moseley, *in press*).

The role of distorted body perception in long standing pain problems has received some attention recently (Lotze and Moseley, 2007; McCabe and Blake, 2008; Swart et al., 2009). In fact, some have proposed that chronic pain is a result of incongruence between predicted and actual proprioceptive feedback, by virtue of disrupted body maps (Harris, 1999; McCabe et al., 2005a,b, 2007). This is a contentious issue that remains to be supported or refuted (see Moseley and Gandevia, 2005; McCabe et al., 2005a,b). The potential importance of changes in bodily awareness may go

beyond symptoms to top-down modulation of tissue function – recent work has shown that experimental disruption of body awareness can alter tissue temperature Moseley et al., 2008a and swelling (Moseley et al., 2008b).

Given our incomplete understanding of cortical function and its inherent complexity it is possible to make a number of predictions to describe how the observed brain changes might cause or perpetuate the CLBP experience that all possess a degree of plausibility. Any such predictions are currently speculative. Most studies of brain function are small and cross sectional and some of the variability between findings and the relationships within the data will be the result of factors such as divergent methodology and simple lack of statistical power. However, what can be concluded with some confidence is that CLBP is characterised by alterations in cortical structure and function and that these alterations demonstrate relationships with the clinical manifestations of the condition. Also the observations we have made here are supported by our current understanding of brain function and each observation has supportive experimental evidence. One could argue then, that the manifestations of cortical changes at least make rehabilitation more difficult, and indeed may prove to contribute to the problem, as well as the failure of common treatment approaches. As such, it seems reasonable to suggest that the brain may be a legitimate target for new therapies.

4. Training the brain of people with CLBP

Treatment approaches that explicitly target brain function have already been tested in other chronic pain problems, such as complex regional pain syndrome (CRPS) and phantom limb pain (PLP), which are also characterised by significant cortical dysfunction. There is growing evidence that graded motor imagery is an effective treatment for CRPS (Moseley, 2004, 2005, 2006) and PLP (Moseley, 2006) and some indication that mirror visual feedback reduces pain in acute CRPS (McCabe et al., 2003) and in PLP patients (Chan et al., 2007; Mercier and Sirigu, 2009). Sensory discrimination training programmes have also been shown to improve outcome in patients with PLP (Flor et al., 2001) and CRPS (Moseley et al., 2008; Moseley and Wiech, 2009).

Clinicians need to be cautious in generalising these data to the CLBP population. The nature of cortical dysfunction in PLP and CRPS has been more thoroughly investigated and the relationship to clinical status is better understood. Moreover, the management approaches outlined above have focused on patients with unilateral limb pain. The back and limb are obviously functionally distinct, are represented differently in the brain and it is likely that the psychological and social implications of a limb injury are different to those of a low back injury. Significant research still needs to be done before firm recommendations can be made about this type of management approach for patients with CLBP.

We have begun this process by investigating clinical correlates of cortical disruption in the CLBP population (Bray and Moseley, *in press*; Luomajoki and Moseley, *in press*; Moseley, 2008; Wand et al., *in press*) and we are continuing to explore this area. Our group has also started to examine some treatment options. Preliminary data suggest that tactile discrimination training may be helpful, at least for those with reduced tactile acuity. As with CRPS and PLP there are representational changes in S1 and similar deficits in tactile acuity and we are currently investigating the usefulness of a graded tactile discrimination approach for patients with CLBP. Likewise one possible explanation for the success of graded motor imagery relates to gradual activation of movement related networks without eliciting pain (Moseley, 2005). As CLBP is associated with enhanced efficiency of nociceptive networks, it is reasonable to suggest that graded motor imagery may also be helpful in this population, and we have anecdotal data to support this idea. In

addition, the data showing disrupted responses to pain-related cues, sensitivity changes to a variety of stimuli and cortical deactivation failure, raises the possibility that widespread disinhibition is a fundamental issue in the problem of CLBP. This suggests that treatment paradigms that elicit intracortical inhibition, such as tone-pitch recognition, may affect the CLBP experience and we have also begun to explore this approach. Crucially, these are embryonic treatments and they are yet to stand the test of experimental interrogation, yet they are evidence of a new line of enquiry and approach to treatment that is being directed towards the brain, not the back, of people with back pain.

5. Conclusion

High quality evidence suggests that most existing approaches to the management of CLBP have only limited success. CLBP is characterised by a range of structural, functional and neurochemical changes within the brain. In other chronic painful disorders, for example PLP and CRPS, the nature and impact of brain changes are well studied, and treatments that aim to normalise some of these changes have been tested and proven effective at reducing pain and disability. However, for CLBP, this process is in its infancy – we know less about the brain changes themselves and treatments have not been fully developed, nor tested. We are continuing to learn more about the cortical changes apparent in CLBP and the clinical implications of these changes. Our group has begun to focus on developing simple clinical tools for identifying potential cortical disruption in the CLBP population as well as testing cortically orientated treatment approaches for this pernicious problem. We humbly suggest that for those of us interested in better understanding and treating people with CLBP, the challenge is to be both open minded and patient.

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Competing interest

No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subjects of this manuscript.

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