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The effect of pain on cognitive function: a review of clinical and preclinical research

Orla Moriarty^{1,3}, Brian E. McGuire^{2,3}, David P. Finn^{1,3} *

¹Pharmacology and Therapeutics, School of Medicine ²School of Psychology, ³Centre for Pain Research, National University of Ireland, Galway, University Road, Galway, Ireland.

*Address for correspondence and reprint requests:

Dr David P. Finn

Pharmacology and Therapeutics,

School of Medicine,

National University of Ireland, Galway,

University Road,

Galway,

Ireland.

Tel: +353 (0)91 495280

Fax: +353 (0)91 525700

Email: David.Finn@nuigalway.ie

Abstract

Cognitive impairment is commonly associated with the pain experience. This impairment represents a major obstacle to daily activities and rehabilitation, especially in the chronic pain population. Here we review clinical and preclinical studies that have investigated pain-related alterations in cognition. These include impaired attentional, executive and general cognitive functioning. We describe the anatomical, neurochemical and molecular substrates common to both cognitive processing and supraspinal pain processing, and present the evidence for their involvement in pain-related cognitive impairment. We also examine the added complexity of cognitive impairment caused by analgesic medications and how this can further impact on morbidity in chronic pain patients. The need for a better understanding of the mechanisms of both pain-induced and treatment-related cognitive impairment is highlighted. Further research in this area will aid our understanding of patient symptoms and their underlying pathophysiology, ultimately leading to increased provision of guided therapy.

Keywords: Pain; Nociception; Analgesia; Cognition; Learning; Memory; Attention; Executive Function; Brain; Rat; Human

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1. Introduction

Pain is a subjective, multidimensional experience that can have a marked impact on both the physiological and psychological state of an individual. The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (IASP Task Force on Taxonomy, 1994). This definition is based on the concept of pain as a perception rather than as a purely sensory modality, and takes into account the fact that for pain to be consciously experienced, cognitive processing is required. Melzack and Casey’s (1968) division of pain into sensory-discriminative, motivational-affective and cognitive-evaluative dimensions also supports this concept. Chronic pain (defined as pain persisting for 3-6 months or longer) generally exceeds the duration of the precipitating noxious stimulus or injury, and may be neuropathic, inflammatory or idiopathic in nature (Aguggia, 2003). Epidemiological studies have indicated the extent of the problem of chronic pain in the general population. It has been estimated that 19% of adult Europeans suffer from chronic pain of moderate to severe intensity, of which approximately half receive inadequate pain management (Breivik *et al.*, 2006). Chronic pain has bio-psycho-social implications, affecting relationships, capacity for work, mood and quality of life (Hart *et al.*, 2000). Chronic pain patients report disabling limitations on physical function (van Dijk *et al.*, 2009). In addition to sensory symptoms including allodynia (pain in response to a non-nociceptive stimulus) and hyperalgesia (increased pain sensitivity), cognitive functioning is thought to be affected in chronic pain patients. It is hypothesised that because neural systems involved in cognition and pain processing are closely linked, they may modulate one another reciprocally.

Cognition has been described as the brain's acquisition, processing, storage and retrieval of information (Lawlor, 2002). However, cognition may be considered an umbrella term that can also be used to describe integrative neuropsychological processes such as mental imaging, problem-solving and perception, and is pertinent to the experience of emotion and affect. Pain and cognition share an inherent overlap owing to the fact that pain itself has a cognitive-evaluative component, requiring learning, recall of past experiences and active decision making. This should be borne in mind when assessing the effects of pain on cognitive function. For the purposes of this review, we have chosen to focus on the effects of chronic pain on a subset of cognitive domains including; attention, learning and memory, speed of information processing, psychomotor ability and executive function. Loss of function in these domains is likely to impact on the execution of daily tasks and, therefore, negatively affect the individual. Detailed evaluation of the interaction of pain with mood, stress and anxiety, as well as parameters such as coping, disability and quality of life is beyond the scope of this review, but may be found elsewhere (Anton, 2009; Breivik *et al.*, 2006; Campbell *et al.*, ; Dersh *et al.*, 2002; Hart *et al.*, 2003; Jensen *et al.*, 2007; McCracken and Eccleston, 2003; Munoz and Esteve, 2005; Pincus *et al.*, 2007; Vowles and McCracken, 2008). We have also omitted studies that examine the analgesic effects of cognitive interventions (examples include distraction, hypnosis and mindfulness), except where the converse effects of pain on cognition have also been examined, or where the results provide insights into potential mechanisms of pain-induced cognitive impairment. We review the clinical studies which have directly measured cognitive function in chronic pain patients, in an attempt to establish whether chronic pain negatively affects cognition. We examine the neural substrates which may be responsible for impaired cognition during the experience of chronic pain, including the neuroanatomical structures, neurotransmitter systems and other neuromodulators common to pain and cognition. Based on the data available, we put forward

a theoretical model for the mechanisms involved in pain-related cognitive impairment. The manuscript also reviews the limited literature available on cognitive performance in animal models of pain, and we highlight how these and future preclinical studies may contribute to our understanding of pain-cognition interactions. The possible confounding effects of pharmacological treatment with analgesics on cognition are also considered.

2. Clinical studies: Evidence for pain-related cognitive impairment

The increasing prevalence of pain-related illnesses, and their economic and psychological consequences, has resulted in a heightened interest in both the neurobiological mechanisms underpinning pain, and the effects of pain on a range of processes, including cognition. Disruption of cognitive processing has been investigated in a variety of common chronic pain syndromes with studies focusing on a number of different types of cognitive output. The methodology employed in these studies is most commonly a test battery, which may typically include pain questionnaires and numerical rating scales (NRS) and/or visual analogue scales (VAS) to measure pain, coupled with tests of cognition. Cognitive function may be assessed using subjective self-report measures or objectively with formal, empirically validated neuropsychological tests (Ersek *et al.*, 2004). Co-morbid affective disorders (such as depression and anxiety), and the effects of sleep disturbance and medication use are sometimes, but not always, considered and they present an interesting dichotomy in experimental approach. While some researchers may consider these factors integral to the complex experience of chronic pain, others may wish to minimise their confounding effects and choose to exclude patients from research studies based on these factors. Table 1 has been generated following an in depth review of the literature and gives a comprehensive summary of studies which have objectively investigated altered cognitive function in patients with

chronic pain. The majority of the cognitive parameters investigated relate to attention, learning and memory, speed of processing, psychomotor ability and executive function.

2.1 Attention:

Due to its biological salience, pain is an inherently attention-demanding sensory process. Hence, the effects of pain on attention are particularly well studied (Table 1). Chronic pain patients frequently self-report difficulty with attention (Dufton, 1989; Jamison *et al.*, 1988; Kewman *et al.*, 1991; McCracken and Iverson, 2001; Munoz and Esteve, 2005), and empirical studies have also demonstrated attentional deficits in chronic pain patients (Alanoglu *et al.*, 2005; Bosma and Kessels, 2002; Dick *et al.*, 2002; Dick and Rashiq, 2007; Eccleston, 1994; Grace *et al.*, 1999; Grisart and Plaghki, 1999; Oosterman *et al.*, 2010; Ryan *et al.*, 1993; Veldhuijzen *et al.*, 2006a) (see Table 1). Deficits in performance were particularly apparent on attention switching and attentional interference tasks. It is hypothesised that pain competes with other attention-demanding stimuli for limited cognitive resources (Eccleston and Crombez, 1999; Grisart and Van der Linden, 2001). Ongoing pain stimuli may impair top-down attentional control mechanisms which filter out task-irrelevant stimuli resulting in impaired task performance (Legrain *et al.*, 2009a). This theory may represent one possible mechanism for cognitive impairment associated with chronic pain. Deficits in attention have been demonstrated in a wide variety of chronic pain disorders including fibromyalgia (FM, a disorder of unknown aetiology, characterized by chronic musculoskeletal pain and tactile allodynia), diabetic neuropathy, chronic lower back pain, Whiplash Associated Disorder (WAD), as well as in heterogeneous groups of chronic pain patients (Table 1). Studies specifically assessing migraine patients generally fail to demonstrate pain related deficits in attention (Table 1). This may be due to decreased pain-related interference between migraine attacks.

2.2 Learning, memory and general cognition:

Learning and memory have been evaluated psychometrically in chronic pain patients, with patients performing poorly compared with controls on parameters including spatial (Dick and Rashiq, 2007; Luerding *et al.*, 2008) and verbal (Antepohl *et al.*, 2003; Bosma and Kessels, 2002; Grace *et al.*, 1999; Oosterman *et al.*, 2010; Park *et al.*, 2001; Weiner *et al.*, 2006) working memory capacity and recall, recognition memory (Park *et al.*, 2001), long-term spatial memory (Luerding *et al.*, 2008). Memory impairments have been shown in a number of diseases of which chronic pain is a symptom, but are particularly prevalent in FM (Glass, 2009; Table 1). Studies of memory in chronic pain patients have largely tested parameters of working (explicit) memory. Implicit (semantic, procedural, and conditioned) memory is generally considered an automated process, less likely to be affected by the presence of chronic pain (Grisart and Van der Linden, 2001). However, FM patients have also shown deficits in semantic memory (verbal knowledge) tasks where they were required to select the antonym or synonym of a presented word (Park *et al.*, 2001). Fatigue and depression are also common in FM, however, and may affect performance in these cognitive domains.

Chronic pain patients also perform poorly compared with controls on general screening measures of cognition, such as the Mini Mental State Exam (MMSE) (Meyer *et al.*, 2000; Oosterman *et al.*, 2010; Weiner *et al.*, 2006), Cognitive Capacity Screening Exam (CCSE) (Meyer *et al.*, 2000), and electroencephalographic measurement of the P300 event related potential (Alanoglu *et al.*, 2005). Furthermore, the prevalence of clinically relevant cognitive impairment (measured as an MMSE score ≤ 24) was higher in chronic pain patients in comparison with the general population (Povedano *et al.*, 2007; Rodriguez-Andreu *et al.*, 2009). As is the case for attentional tasks, deficits were observed across a variety chronic

pain conditions (Table 1). FM patients achieved significantly lower scores on the MMSE than patients with a diagnosis of neuropathic or mixed pain (Rodriguez-Andreu *et al.*, 2009). In that study, there did not appear to be a direct link between impaired performance and pain severity. An inverse relationship between MMSE, or CCSE, performance and pain scores in chronic pain patients has not been reported. However, other studies have shown an inverse correlation between pain scores and cognitive performance (see Table 1).

2.3 Speed of information processing and psychomotor ability:

Chronic pain patients display slower reaction times than matched controls in a variety of standardised cognitive tests (Alanoglu *et al.*, 2005; Antepohl *et al.*, 2003; Biessels *et al.*, 2007; Calandre *et al.*, 2002; Harman and Ruyak, 2005; Sjogren *et al.*, 2005), in particular on tests related to psychomotor ability (Harman and Ruyak, 2005; Lee *et al.*, 2010; Ryan, 2005; Ryan *et al.*, 1993; Ryan *et al.*, 1992). Impaired perceptual learning ability has also been shown in chronic pain patients (Maihofner and DeCol, 2007). These results suggest a common pattern of impaired perceptual-motor coordination in chronic pain (Table 1). The studies in Table 1 appear to suggest a high prevalence of psychomotor dysfunction in diabetic neuropathy; however, it should be noted that this parameter has not been routinely tested in other chronic pain disorders.

2.4 Executive Function:

Executive function loosely defines neurological processes that enable more complex cognitive tasks such as planning, organisation, control of conflicting thoughts, goal-directed behaviour, initiation of action and assessing the consequences of actions. Clinically,

executive function is assessed using interference tasks such as the Wisconsin Card Sorting Test (Grant and Berg, 1948), the Process Dissociation Procedure (Jacoby, 1991), and flexibility tasks such as the Trail Making Test (Adjutant General's Office, 1944). Patient performances on these tests appear to show that controlled executive-type functions are affected by chronic pain (Karp *et al.*, 2006; Ryan *et al.*, 1993; Verdejo-Garcia *et al.*, 2009; Weiner *et al.*, 2006), and may be more severely affected than less complex, automatic processes (for example fixed sequences of operations that do not require higher control) (Grisart and Van der Linden, 2001) (Table 1). Complex tests of attention, such as those that involve interference or attention switching, may require executive function and chronic pain patients perform poorly on such tests (Bosma and Kessels, 2002; Eccleston, 1994; Karp *et al.*, 2006; Ryan *et al.*, 1993). For example, Eccleston (1994) showed that pain affected performance on an attentional-interference task, but only when the task was at its most complex. Studies by Suhr (2003) and Scherder *et al.* (2008), however, failed to show any executive function deficits in chronic pain patients. A study by Oosterman and colleagues (2009) actually found a positive relationship between self-reported pain and executive function (increased pain levels associated with improved cognitive function). However, this study did not include a pain-free control group and was carried out specifically in elderly pain patients (ages 84.6 ± 0.5 years). Emotional decision making and emotional self-regulation are also thought to involve higher executive functioning and appear to be compromised in some chronic pain patients (Apkarian *et al.*, 2004a; Solberg Nes *et al.*, 2009; Verdejo-Garcia *et al.*, 2009). Interestingly, a study by Veldhuijzen *et al.* (2006a) also found that chronic pain patients, while showing increased errors in an attentional task, had shorter response times than healthy controls. Together, these findings indicate that chronic pain may be associated with increased impulsivity or impaired attentional control. Executive function is under control of frontal brain regions that are also involved in pain processing. The potential

forebrain mechanisms by which pain may affect executive function are discussed in a later section. Deficits in executive function have been shown in a number of chronic pain disorders, and do not appear to follow a disease-specific pattern (Table 1). However, impaired emotional decision making was found to be impaired in patients with chronic back pain but not in patients suffering from complex regional pain syndrome (Apkarian *et al.*, 2004a).

2.5 Appraisal and caveats of clinical literature:

Overall, the clinical studies published to date provide a strong basis for the theory that cognitive function is impaired in chronic pain patients compared with controls, and with the general healthy population. Deficits in a number of cognitive parameters have been shown using several well validated psychometric tests. However, it is important to exercise caution in interpreting these results, due to differences in experimental conditions and control measures, and the diversity of pain states examined and their aetiology.

A number of studies have shown an inverse relationship between pain and cognitive performance in chronic pain patients (see Table 1), however, many of these studies did not include a non-pain comparative group. Significant negative effects of pain on cognition have also been reported by Soderfjell *et al.* (2006), but these authors examined only undiagnosed self-reported pain and the study did not include an analysis of the effects of chronicity. Studies that show effects of experimental pain on cognition in healthy control subjects (Babiloni *et al.*, 2004; Crombez *et al.*, 1994; Crombez *et al.*, 1996, 1998; Legrain *et al.*, 2009b; Moore *et al.*, 2009; Vancleef and Peters, 2006; Walker 1971) have been omitted from Table 1. However, it is worth noting that such studies may provide an opportunity to design more carefully controlled studies than those involving clinical pain populations and, as such,

they may allow stronger conclusions to be drawn regarding the effects of pain *per se* on cognitive functioning. Research should, however, consider the multidimensional nature of pain (see Introduction), and experimental pain studies can be criticised because of their limited ability to accurately model motivational-affective and evaluative aspects of pain (Gagliese, 2007). Furthermore, the effect of chronic pain on neuropsychological function may be cumulative, and quantitatively different from acute/experimental pain (May, 2008).

There are also studies that report no association between chronic pain and impaired cognitive function (Bell *et al.*, 1999; Landro *et al.*, 1997; Pincus *et al.*, 1998; Scherder *et al.*, 2008; Suhr, 2003). Furthermore, functional deficits may manifest in the absence of measurable cognitive impairment. For example, a study by Veldhuijzen *et al.* (2006b) in chronic pain patients found functional disability in a cognitively-demanding driving assessment, but no impairment in laboratory tests of related cognitive parameters (tracking, divided attention and memory). There is some evidence that the level of pain-related interference increases as task difficulty increases (Eccleston, 1994), with high-order executive functions specifically affected in some cases (Apkarian *et al.*, 2004a).

The majority of studies presented used a battery of neuropsychological tests to assess cognition (Table 1), or used general screening measures such as the MMSE or CCSE. Deficits were commonly observed in some cognitive domains but not in others, and there is no obvious pattern of common effects between studies (Table 1). FM and diabetic neuropathy appear to be consistently associated with cognitive impairments, though the spectrum of impairments differs between studies (Table 1). Studies which have examined cognitive performance in mixed chronic pain disorders do not provide information on whether specific impairments are more frequently observed in specific disorders. However, the investigation by Apkarian *et al.* (2004a) showed that pain ratings were negatively correlated with impaired performance in one type of chronic pain but not in another (chronic

back pain, not complex regional pain syndrome), suggesting that the type of chronic pain disorder may be important in relation to cognitive effects. In addition, pain-related cognitive impairments may be transient and reversible in some chronic pain conditions such as headache (Meyer *et al.*, 2000). There is a need for comparative studies across chronic pain disorders, to establish whether impairments are indeed pain-related or whether they are a consequence of other disease characteristics. Future studies should also continue to test multiple cognitive domains, with a view to establishing a standard array of cognitive impairments which are likely to be experienced by chronic pain patients.

Research in chronic pain is complicated by the fact that pain is a symptom of many complex disorders such as FM and diabetes, and is frequently co-morbid with affective disorders (anxiety and depression), stress and fatigue. Chronic pain has a bidirectional relationship with these conditions, through effects on neuroendocrine and neurotransmitter systems. Thus, it is possible that symptoms or pathophysiological features that are not related to pain, but which are features of these co-morbidities may also affect the aspects of cognition highlighted above (Austin *et al.*, 2001; Brown *et al.*, 2002; Capuron *et al.*, 2006; Castaneda *et al.*, 2008; Eysenck *et al.*, 2007; Hindmarch, 1998; Lupien *et al.*, 2007). In addition, psychological traits such as hypervigilance and catastrophizing are common in chronic pain patients, and may affect the outcome of cognitive tests. In view of these factors, it is difficult to draw conclusions with respect to the direct effect of pain on cognitive function. Disease symptoms, other than psychiatric symptoms, may also affect patients' ability to perform well on tests of cognitive function. For example, diabetic neuropathy occurs as a result of hyperglycemia-induced nerve damage which can also affect motor neurons. This damage may, in part, explain poor performance on tests of psychomotor ability in these patients. Motor impairment may also explain the dissociation between impaired driving ability and lack of impairment in laboratory tests of cognition observed by Veldhuijzen *et al.* (2006b), described above.

Certain pain conditions may also be more likely to occur in different demographic groups. For example, fibromyalgia is more likely to occur in women than in men, and arthritis is more prevalent in older adults. Age and gender have been shown to influence cognitive performance (see Table 1), though these variables are commonly accounted for statistically. In addition, studies examining pain-related cognitive effects have been carried out in specific demographic groups such as older adults (Karp *et al.*, 2006; Weiner *et al.*, 2006), female patients only (Alanoglu *et al.*, 2003, Park *et al.*, 2001; Verdejo-Garcia *et al.*, 2009) and male patients only (Lee *et al.*, 2010). Pain chronicity or duration of chronic pain illness may also be a factor in the relationship between pain and cognition. Eccleston *et al.* (1994) and Alanoglu *et al.* (2005) found that pain chronicity was not associated with differences in cognitive function, whereas other studies have shown that duration of illness (migraine, diabetes and fibromyalgia, CRPS and chronic back pain) was inversely related to cognitive performance (Apkarian *et al.*, 2004a; Calandre *et al.*, 2002; Ryan *et al.*, 2005; Verdejo-Garcia *et al.*, 2009), though analyses may also adjust for chronicity. However, the majority of studies did not consider this variable when assessing the effects of pain on cognitive function. There is a paucity of studies which longitudinally assess cognitive function in chronic pain patients. This type of study would be useful to determine whether cognitive dysfunction worsens over time. The use of medication is common in chronic pain patients, and may impact on cognitive function (see section 6 below for discussion).

Studies which examine cognition in chronic pain patients may attempt to account, experimentally (matching, inclusion/exclusion criteria) or statistically, for co-morbidities, age, gender, pain chronicity and medication use, although as discussed previously this may not provide a realistic representation of typical chronic pain populations. Importantly, irrespective of these additional factors, a number of studies have shown a direct correlation between the level of cognitive dysfunction and pain ratings in chronic pain patients (see

Table 1). In addition, and as discussed further in section 6 below, improvements in cognitive performance in patients suffering from chronic pain have been observed following chronic analgesic treatment (Tassain *et al.*, 2003; Jamison *et al.*, 2003). Together, these studies may provide the best clinical evidence for pain-related cognitive impairment.

3. Clinical studies: Insights into potential mechanisms involved in pain-related cognitive impairment

Although the precise mechanisms have yet to be elucidated, several theories have emerged regarding the mechanisms mediating cognitive impairment in conditions of persistent pain. As discussed in the previous section, it may be argued that the cognitive impairments observed in chronic pain may simply be a consequence of the division of limited resources in discrete brain regions. The persistent nociceptive inputs associated with chronic pain may compete with other sensory inputs resulting in reduced cognitive performance (Eccleston and Crombez, 1999). Hart and colleagues (2000) proposed that neuroplastic changes occur in chronic pain and that such neural rewiring or reorganisation in the brain interferes with normal cognitive functioning. These authors also suggested that neurochemical mediators, released during chronic pain, may have a negative effect on cognitive processing. The neuroanatomical and neurochemical substrates at which pain and cognitive processing systems overlap (and are likely to interact with one another) will be discussed in light of these possible mechanisms.

3.1 Human Imaging Studies

3.1.1 Functional Neuroimaging

Studies using neuroimaging techniques, including electroencephalography (EEG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), have greatly advanced our understanding of the interaction between pain and cognitive processing at a neuroanatomical level. The pain experience has been described as the output of an integrated neural network or “neuromatrix” (Melzack, 1999). Somatosensory cortical areas 1 and 2 (SI and SII), the insular cortex (IC), the thalamus, the prefrontal cortex (PFC) and the anterior cingulate cortex (ACC) have been identified as the six brain regions most commonly activated during pain processing (Apkarian *et al.*, 2005). The periaqueductal gray (PAG), basal ganglia, cerebellum, amygdala and hippocampus have also, though less consistently, shown pain-related activation.

Components of the pain neuromatrix are also critical in the processing of cognitive information. The ACC receives input from limbic regions such as the thalamus, the hippocampus and the amygdala, and its role in control of selective attention, working memory and error awareness has been demonstrated using fMRI (Klein *et al.*, 2007). Buffington *et al.* (2005) examined activation of the ACC in healthy subjects and chronic pain patients subjected to an acute noxious stimulus, whilst carrying out a continuous performance task requiring sustained attention. ACC activations were modulated by acute pain and by the sustained attention task. The authors describe an inverse relationship between two distinct components of activation, one thought to relate to sustained attention and one to acute pain stimulation. The component related to acute pain stimulation was activated to a greater extent in chronic pain patients both before and after painful stimulation. In addition, ACC activation relating to the attentional task performance was localised differently in patients and controls. These results suggest that chronic pain alters normal processing in the ACC, which could account for deficits in cognitive function. Frankenstein *et al.* (2001) used fMRI to study healthy subjects undergoing the cold pressor test whilst performing a distracting verbal task.

Results showed that separate areas of the ACC responded to the painful stimulus and to the distracting task. However, a subregion in the perigenual area of the ACC was co-activated in both conditions, and this finding has been replicated in other imaging studies of experimental pain in healthy subjects (Bantick *et al.*, 2002; Valet *et al.*, 2004). In addition, pain-evoked activity in the ACC can be altered in healthy volunteers by hypnotic suggestions (Faymonville *et al.*, 2000; Rainville *et al.*, 1997), pain anxiety (Ploghaus *et al.*, 2001) and anticipation of pain (Hsieh *et al.*, 1999). Competition between pain and cognition for processing resources in the ACC may result in a reduced functional capacity, thereby reducing cognitive ability in pain states.

The IC shows somatotopic organisation (Brooks *et al.*, 2005), is a component of the limbic system, and is activated by the experience of emotions such as happiness, sadness, anger, fear and disgust (Damasio *et al.*, 2000; Phillips *et al.*, 1997). The IC is interconnected with the entorhinal cortex and the amygdala (Insausti *et al.*, 1997; Shi and Cassell, 1998) and is therefore presumed to play a role in affective processing of pain and pain control. Activation of the IC caused by experimental thermal pain was reduced when subjects were distracted by a visual stimulus (Brooks *et al.*, 2002). Other distracting tasks were also found to reduce pain-induced activity in the IC in healthy subjects (Bantick *et al.*, 2002; Longe *et al.*, 2001). Conversely, increased IC activation in pain could be associated with impaired cognitive performance, particularly in emotionally demanding tasks, such as the Iowa gambling task, though this hypothesis has not yet been tested.

The PAG is known to be involved in pain control and is an important component of the endogenous descending inhibitory pain pathway. Imaging studies have shown altered activity in the PAG during simultaneous cognitive and evoked-pain processing in healthy participants. Performance of a maze task (Petrovic *et al.*, 2000) or directing attention to a

painful stimulus (Tracey *et al.*, 2002) reduced pain-induced activation in the PAG, but it is unclear whether pain may modulate cognitive function through this region.

Single positron emission computed tomography (SPECT) has shown alterations in cerebral blood flow (hypoperfusion) in migraine patients when compared with healthy controls (Calandre *et al.*, 2002). Areas of hypoperfusion were diffuse, but prominent in frontal and parietal regions. Altered cerebral blood flow was found to be associated with significant impairment on cognitive tasks of verbal and visual memory. In a separate study, a heterogeneous sample of chronic pain patients showed altered EEG patterns, compared to controls when carrying out a visual task and attending to irrelevant stimuli (Veldhuijzen *et al.*, 2006a). These authors predicted that as task difficulty increased, the amplitude of P300 event-related potentials associated with task stimuli would increase and the amplitude of those associated with task-irrelevant stimuli would decrease. However, chronic pain patients did not show a decrease in response to task-irrelevant stimuli, suggesting impaired allocation of attentional resources in these patients. A further EEG study by Tiemann and colleagues (2010) in healthy subjects found that as pain-induced gamma oscillations increased, task-related visual gamma oscillations decreased. This neural response was associated with impaired task performance in a subset of subjects.

These studies effectively highlight the overlapping brain regions involved in pain and cognitive processes and support the “division of resource” theory for cognitive impairment in chronic pain. However, it is important to note that a number of these studies are concerned primarily with psychoanalgesic effects of cognitive interventions, and have not directly examined the negative effect of pain on cognition. In addition, the majority of these studies were performed in healthy volunteers subjected to experimental pain under laboratory conditions. As discussed in section 2.5, this type of experimental pain may not provide information relevant to the clinical chronic pain situation. There is a need, therefore, for

further functional imaging studies examining brain activation in chronic pain patients carrying out cognitive tasks.

3.1.2 Brain morphology

Gross changes in brain morphology, and more subtle regional and cellular morphological changes, have been reported in various types of chronic pain. Patients suffering from chronic lower back pain and FM, for example, have significantly less total grey matter volume than age-matched healthy controls (Apkarian *et al.*, 2004b; Kuchinad *et al.*, 2007; Schweinhardt *et al.*, 2008; Wood *et al.*, 2009). A reduction in grey matter is a feature of ageing, which is inherently associated with cognitive decline and in particular in the speed of information processing and executive functions (Salthouse, 1996; Salthouse *et al.*, 1998). Loss of grey matter in chronic pain patients occurs at an increased rate compared with healthy controls and this may represent an acceleration of ageing-induced grey matter loss. Loss of grey matter may contribute to some of the cognitive deficits that have been described in chronic pain patients. Voxel-based morphometry has been used to examine region-specific changes in grey matter volume in chronic pain patients, with regions such as the IC, the ACC and the dorsolateral PFC consistently showing reduced volumes (Apkarian *et al.*, 2004b; Kuchinad *et al.*, 2007; Luerding *et al.*, 2008; May, 2008; Schmidt-Wilcke *et al.*, 2006; Schmidt-Wilcke *et al.*, 2005; Schmidt-Wilcke *et al.*, 2007; Valfre *et al.*, 2008). As discussed earlier in this section, the IC and the ACC are commonly implicated in both pain-experience processing and cognitive processing. The PFC is also critically involved in pain processing, comprising part of the pain neuromatrix, but in addition is involved in working memory and recognition, and is the neural centre of executive functioning (Kouneiher *et al.*, 2009; Robbins, 1996). Therefore, grey matter changes in the frontal or cingulate cortex could be associated with

impaired working memory or executive functioning. Luerding and colleagues (2008) investigated this possibility by examining correlations between grey matter volumes and neuropsychological performance in chronic pain patients. They found that visual working memory was positively correlated with grey matter volume in the left dorsolateral PFC. Unfortunately, these techniques do not allow us to determine whether pain-related variance in grey matter results from changes in the number of neurons, interneurons or glia, or from changes in cell size.

4. Preclinical studies: Evidence for pain-related cognitive impairment

Pre-clinical studies provide an opportunity to further explore the mechanisms mediating pain-related impairment of cognition. However, this type of basic research has been under-utilised, with few published studies attempting to model the clinical phenomenon of pain-related cognitive impairment in laboratory animals despite the availability of well-validated animal models of pain and cognitive impairment.

There is some evidence that pain impacts negatively on cognition in rodents (see Table 2). Studies by Cain and colleagues (1997) and Lindner and colleagues (1999) found that complete Freund's adjuvant (CFA)-induced inflammatory pain was associated with impaired performance on a delayed nonmatching-to-position lever-press task, which is sensitive to deficits in learning, memory and attention. Millecamps et al. (2004) reported a decrease in non-selective, non-sustained attention in a rat model of visceral inflammatory pain. 2,4,6-trinitrobenzene was used to induce colitis and attentional level was assessed using a novel-object paradigm. Control rats spent a significantly larger percentage of time exploring the novel object than colitic rats. This finding is consistent with another study which investigated attention in a model of tonic persistent pain in rats. Animals treated with formalin showed

decreased attention in an operant nose-poke task (Boyette-Davis *et al.*, 2008). Pais-Vieira and colleagues (2009a) also showed that correct responding in a nose-poke task decreased and the number of omissions increased, following induction of chronic inflammatory pain with CFA. Work in our own laboratory (Ford *et al.*, 2008) has also suggested an inverse relationship between selective attention towards an unfamiliar object and formalin-evoked nociceptive behaviour in rats.

Inflammatory pain has been shown to affect the performance of rats in a gambling task which is thought to be analogous to the Iowa gambling task and assesses emotional decision making (Zeeb *et al.*, 2009). In two rat models of monoarthritis (intra-articular kaolin and carrageenan to the knee joint or CFA to the tibiotarsal joint of the hindpaw), pain responding was associated with a preference for a “high risk” lever associated with larger but more infrequent rewards than the alternative lever (Ji *et al.*, 2010; Pais-Vieira *et al.*, 2009b). These findings parallel the clinical investigations of Verdejo-Garcia *et al.* (2009) and Apkarian *et al.*, (2004a), in which chronic pain patients showed impaired learning in the Iowa gambling task. However, the “emotional” processing component may be different between species.

Cognitive performance has also been investigated in animal models of chronic neuropathic pain. Streptozotocin (STZ)-induced diabetes in rats was found to be associated with impaired spatial learning in the Morris water maze (Biessels *et al.*, 1996; Biessels *et al.*, 1998; Kamal *et al.*, 2000). STZ-induced diabetes is likely to have been associated with painful neuropathy; however this was not directly assessed in these studies, and warrants further investigation. A recent study by Hu *et al.* (2010) found impairments in spatial learning and memory in Morris water maze following L5 spinal nerve transection as a model of neuropathic pain in the rat. Furthermore, Leite-Almeida *et al.* (2009) described impaired behavioural flexibility in a rat model of neuropathic pain. In this experiment, spared nerve injury (SNI) was used to model chronic neuropathic pain. Nerve-injured rats showed impairment in the spatial reversal task

of the Morris Water Maze. In the reversal task, rats are required to learn the position of a hidden platform according to spatial cues (as in the traditional learning task) and once the position was learned, the platform was moved to a new location. Control rats, with intact behavioural flexibility, rapidly learned the new location while impaired rats continued to explore the old location. This type of behavioural test is somewhat analogous to clinical tests of executive function, and so the preclinical models show some similarity to clinical studies that found impaired executive function in chronic pain patients. On the other hand, Suzuki et al. (2007) found that contextual aversive memory was not affected in mice that had undergone spinal nerve ligation (SNL) surgery as a model of neuropathic pain. To our knowledge, these are the first and only studies to examine *in vivo*, cognitive performance in animal models of neuropathic pain and so represent an important contribution to the field.

The majority of these studies show that pain-related cognitive impairment can be modelled in laboratory animals, and suggest that this phenomenon should be exploited in future research to elucidate the neural mechanisms involved. Tests of cognition in animal models are largely based on spatial learning and memory or attention, which have also been shown to be impaired in chronic pain patients (see Table 1). However, in contrast to the clinical studies, assessment of cognition in animal subjects is highly dependent on locomotor activity and appetitive responding, both of which are likely to be affected in models of chronic pain. Neuropathic and inflammatory pain models were found to be associated with impaired motor function (Cain *et al.*, 1997; Lindner *et al.*, 1999; Leite-Almeida *et al.*, 2009). Leite-Almeida et al. (2009) avoided the confounding effect of decreased locomotor activity in the water maze cognitive task by measuring the path length. Cain et al. (1997) and Lindner et al. (1999) did not account for the effect of impaired locomotor activity on cognitive performance, and as such, the effect of pain on task performance is difficult to interpret. Chronic pain models are also frequently associated with the expression of depressive-like symptoms, such as

increased immobility time in the forced swim test (Hu *et al.*, 2010; Leite-Almeida *et al.*, 2009; Suzuki *et al.*, 2007). Anhedonia may also be a feature of animal models of chronic pain, as CFA-treated rats tended to demonstrate a decrease in sucrose consumption (Shi *et al.*, 2010). It is reasonable to assume, therefore, that motivation to earn food rewards (necessary for operant cognitive tasks), to explore (necessary for object exploration tasks), and to escape aversive situations (necessary for water maze and passive avoidance tests of cognition) may also be impaired in models of chronic pain. In the study by Millecamps *et al.* (2004) there was no decrease in total object exploration in colitic rats, which suggests motivation to explore was not affected in this pain model. In operant tasks, motivation is generally assessed within the test protocol by measuring the number of trials initiated by the rat (Pais-Vieira *et al.*, 2009a) or latency to retrieve food rewards (Boyette-Davis *et al.*, 2008). Although pain did not affect these measures, impaired motivation as a potential confound cannot be completely ruled out.

Despite these limitations, the preclinical animal literature shows similarities with the clinical literature. It appears that high-order executive-type functions may be most severely affected in pre-clinical models (Leite-Almeida *et al.*, 2009), as is the case for clinical studies (see section 2). In addition pain relief using analgesic drugs appears to reverse cognitive impairments observed in chronic pain models (Boyette-Davis *et al.*, 2008; Cain *et al.*, 1997; Hu *et al.*, 2010; Lindner *et al.*, 1999; Millecamps *et al.*, 2004). Thus, results in preclinical models parallel those from clinical studies of pain-related cognitive impairment, suggesting that further examination of the neural mechanisms in animal models may translate to humans. Future animal studies should adopt a similar approach to clinical studies by assessing a variety of different cognitive domains in a variety of different pain models, and should also investigate whether the expression of chronic pain-like behaviours is negatively correlated with impaired cognitive performance.

5. Pre-clinical studies: Insights into potential mechanisms involved in pain-related cognitive impairment

5.1 Brain morphology and electrophysiology

Animal models of neuropathic pain, including SNI, SNL and chronic constriction injury (CCI) models have been used to examine pain-related changes in brain morphology. A recent study by Seminowicz et al. (2009) used MRI to examine pain-related alterations in the brain of SNI rats. These authors found that decreases in cortical volume in SI and SII regions, the ACC and the IC correlated with the degree of mechanical hyperalgesia. They also showed that SNI rats had decreased prefrontal cortex volume. The decrease in volume was associated with onset of anxiety behaviours in this experiment; however, as discussed in the previous section, the prefrontal cortex is also important in cognition, with particular relevance to executive function.

Pain-related changes at a cellular level have also been examined in rodent models of chronic pain. Cell-type specific increases in firing frequency of neurons in the ACC have been shown following peripheral nerve injury in mice (Cao *et al.*, 2009). Length and branching of basal dendrites and spine density were increased in pyramidal neurons in acute slices of the medial PFC contralateral to nerve injury in the SNI model (Metz *et al.*, 2009). It is possible that these anatomical changes in the PFC may contribute to cognitive impairment, in particular impaired flexibility such as that described by Leite-Almeida and colleagues (2009) following SNI (see previous section). Goncalves et al. (2008) have also shown increases in amygdalar volume and increased neuronal proliferation in the amygdala of SNI rats, while Ikeda et al. (2007) demonstrated an increase in the amplitude of evoked post-synaptic potentials in central amygdala neurons in SNL rats, compared with sham controls. An elegant

electrophysiological study by Ji et al. (2010) has recently demonstrated that interaction between the amygdala and the PFC contributes to pain-related cognitive impairment in a rodent gambling task. Arthritic pain-related behaviour was associated with impaired performance on the task, as well as increased neuronal excitability and synaptic transmission in the basolateral nucleus of the amygdala. Pharmacological deactivation of the basolateral amygdala restored normal task performance and increased activity in neurons of the medial PFC. Thus, the authors propose that an “amygdala-driven” deactivation of the PFC is responsible for pain-related cognitive impairment in this task. These results provide evidence for pain-induced alterations in plasticity and suggest that there may be a cellular basis for the cognitive impairments associated with chronic pain. The study by Ji et al. (2010) is particularly important as it is the first to propose a mechanism that directly relates pain to cognitive impairment by combining behavioural, electrophysiological and pharmacological approaches.

The ACC has been examined in relation to pain-related memory acquisition and affective pain processing in animal models. Conditioned place-avoidance paradigms give animals free access to a dark (non-aversive) and a light (aversive) chamber. A noxious stimulus is applied when animals are in the preferred dark chamber causing the animals to move from the dark chamber to the light chamber, and to avoid the dark chamber (avoidance). This type of experiment is used to model cognitive-affective aspects of pain processing. Inflammatory pain (CFA, formalin) and neuropathic pain (SNL model) increase short-term avoidance behaviour following painful stimulation of the injured paw, compared with control animals (LaBuda and Fuchs, 2000; Pedersen and Blackburn-Munro, 2006). Lesion of rostral ACC neurons reverses formalin-induced conditioned place avoidance but does not affect nociceptive behaviours (lifting, flinching etc.), thus implicating the ACC in affective pain processing but not in sensory processing (Johansen *et al.*, 2001). Electrical stimulation of the

ACC also resulted in a reversal of avoidance behaviour in a rat model of neuropathic pain (LaBuda and Fuchs, 2005). Scopolamine, a cholinergic antagonist known to impair learning and memory, injected directly into the ACC, impairs pain-related memory acquisition in the rat (Ortega-Legaspi *et al.*, 2003).

The amygdala is highly involved in pain processing and is also a component of the limbic system. It is therefore thought to be important in the affective component of pain. Decreased neurotransmission in the amygdala, by administration of the Gamma-aminobutyric acid (GABA)_A receptor agonist muscimol or lesion of the central nucleus, has been shown to attenuate pain-induced avoidance behaviour i.e. impaired affective processing of pain (Pedersen *et al.*, 2007).

Although these latter studies are of relevance to memory acquisition, they are also associated with an affective component making it difficult to determine conclusively whether the pain-related deficits observed relate specifically to cognition *per se* or to altered affective state of the animal.

The hippocampus is traditionally associated with learning and memory functions. In particular, it is believed to facilitate memory consolidation via long term potentiation (LTP). LTP is a type of synaptic plasticity in which synaptic function is enhanced following a high frequency burst of presynaptic stimulation. *Ex vivo* electrophysiology studies show that LTP is impaired in hippocampal slices from nerve injured mice (Kodama *et al.*, 2007). Subregions of the hippocampal slices were stimulated and recording electrodes measured the field excitatory post synaptic potentials (fEPSPs) before and during high frequency conditioning stimuli to induce LTP. The procedure is considered a basic cellular model for learning and memory, and the pain-related reduction in LTP may relate to the cognitive disturbances associated with chronic pain. Impaired LTP was also observed in slices taken from diabetic

rats (Kamal *et al.*, 1999). Again this result may mirror cognitive disturbances seen in the clinical diabetic population. However, animals were not tested for symptoms of diabetic neuropathy and, as such; decreased LTP in this study cannot be conclusively related to pain. Duric and McCarson (2006) found that pain acts as a stressor to decrease neurogenesis and expression of brain derived neurotrophic factor (BDNF) in the rodent hippocampus. Impaired neurogenesis in this region would likely have a negative effect on learning and memory.

5.2 Neurotransmitters and receptors in pain and cognition

Several neurotransmitter systems are commonly involved in both pain processing and cognition. Glutamate transmission through the NMDA receptor is essential for learning and memory through LTP (Brown *et al.*, 1988; Rison and Stanton, 1995). NMDA receptors are also implicated in central sensitization and wind-up (Scholz and Woolf, 2002). Central sensitization and wind-up involve repeated high-frequency stimulation of nociceptors to increase spinal reflexes and excitability of central nociceptive circuits, a process similar to LTP. Central sensitization is thought to be a key step in the transition between acute and chronic pain. Pain-induced synaptic plasticity has also been shown to occur in higher brain regions with known roles in cognitive function. Plasticity, induced by high-frequency pain stimuli, was enhanced in the amygdala (Bird *et al.*, 2005; Fu *et al.*, 2008; Neugebauer *et al.*, 2003), the ACC (Zhuo, 2006, 2007) and the hippocampus (Zhao *et al.*, 2009) in rodent models of prolonged inflammatory pain. Pain was also associated with increased synaptic efficacy in the hippocampus and the amygdala (Ji *et al.*, 2010; Zhao *et al.*, 2009). Furthermore, the size of synaptic connections was increased and fEPSP waveform shape was altered in the hippocampus in inflammatory pain in rodents (Zhao *et al.*, 2009). It is unclear whether this supraspinal pain-induced plasticity is an extension of the central sensitization that occurs in the spinal cord, though the critical involvement of NMDA (Bird *et al.*, 2005;

Fu *et al.*, 2008; Zhuo, 2006, 2007), AMPA (Zhao *et al.*, 2009) and metabotropic (Ji *et al.*, 2010; Neugebauer *et al.*, 2003) glutamate receptors suggests some mechanistic similarity. One possibility is that pain-induced synaptic plasticity co-occurring with learning/memory-related LTP could result in an overall interference effect which might account for cognitive impairment at a molecular level. Analgesic drugs targeting the glutamatergic system are limited by their cognitive effects. NMDA receptor antagonists such as ketamine show analgesic activity, but also cause CNS effects including visual and auditory disturbances and hallucinations, feelings of unreality and feelings of detachment from the body (Chizh and Headley, 2005). Blockade of metabotropic glutamate receptors (mGluR1 subtype with the selective antagonist A-841720) has been shown to reduce inflammatory pain and allodynia in animal models but impaired function in the Y-maze and water maze tests of cognition (El-Kouhen *et al.*, 2006).

GABA is an inhibitory neurotransmitter and can dampen neuronal activity by inhibiting the release of other neurotransmitters (Enna and McCarson, 2006). GABA can therefore slow sensory transmission and reduce perceived pain. In particular, loss of the inhibitory function of GABA in the spinal cord may contribute to pathological pain (Enna and McCarson, 2006). As GABA is a ubiquitous transmitter, it can also slow cognitive processes and cause sedation, linking pain and cognitive systems. Hyperactivation of the basolateral amygdala in an inflammatory pain model increased GABAergic tone in the prefrontal cortex, and was associated with pain-induced impairment on an emotional decision-making task in rats (Ji *et al.*, 2010). GABA receptor agonists have analgesic efficacy in acute and neuropathic pain models (Malan *et al.*, 2002), but sedative effects and impaired locomotor activity have limited their use as therapeutic agents. Targeting specific subtypes of GABA_A receptors (containing $\alpha 2$ and/or $\alpha 3$ subunits) reduced inflammatory and nociceptive pain without causing adverse sedative effects (Knabl *et al.*, 2008; Mohler, 2009), and selective inverse

agonists of the $\alpha 5$ subunit enhance spatial learning in animal models (Maubach, 2003; Mohler, 2009). Co-expression and activation of these receptor subtypes may be involved in the interaction between pain and cognition, though further research is warranted.

The monoaminergic system plays a key role in expression of pain (Kayser *et al.*, 2007; Mansikka *et al.*, 2005; Millan, 2002; Papaleo *et al.*, 2008; Plaznik *et al.*, 1985), and pain has been shown to be associated with alterations in monoamine signalling in cognitive-associated brain regions (Finn *et al.*, 2006; Omote *et al.*, 1998; Wood, 2008; Wood *et al.*, 2009; Wood and Holman, 2009; Wood *et al.*, 2007a; Wood *et al.*, 2007b). In addition, tricyclic antidepressants (TCAs) which block reuptake of noradrenaline and serotonin are efficacious in the treatment of chronic pain (McClene, 2003). There is also an established role for monoamines in cognitive abilities such as attention (Bunsey and Strupp, 1995; Scholes *et al.*, 2007). Due to their shared role in cognitive function and pain processing, therefore, monoamines may be implicated in the mechanisms underlying pain-related cognitive impairment. However, few studies have investigated monoamine neurotransmitters in both pain and cognition. An early study by Plaznik *et al.* (1985) found that intra-amygdalar serotonin reduced pain behaviour but impaired retention of a passive avoidance response. Mutations in the gene encoding catechol-O-methyltransferase (COMT), an enzyme involved in metabolism of monoamines, resulted in decreased pain sensitivity in transgenic mice, but also impaired working and recognition memory (Papaleo *et al.*, 2008). Pain-related impairment of cognitive performance on a rodent gambling task was found to be associated with a decrease in levels of dopamine and its metabolites in the orbitofrontal cortex (Pais-Vieira *et al.*, 2009b). We have reported a reduction in dopamine and serotonin metabolites in the prefrontal cortex of rats following expression of distraction-induced analgesia (Ford *et al.*, 2008). Dopamine is thought to be important in neuronal integrity (Bozzi and Borrelli, 2002;

Bozzi *et al.*, 2000), and so dysfunctional dopamine signalling may contribute to neuronal loss, which may in turn affect cognition.

Acetylcholine has classically been recognised as one of the most important mediators of cognitive processes such as learning and memory (Drachman and Leavitt, 1974; Lucas-Meunier *et al.*, 2003; McGuire, 1990). There is less evidence supporting a role for cholinergic transmission in pain. However, this transmitter is thought to play a role, both directly and indirectly, in the descending inhibitory control of pain (Millan, 2002), and neuronal nicotinic and muscarinic acetylcholine receptors have been implicated in pain transmission. Studies have shown that nicotinic receptor agonists, such as epibatidine and nicotine itself, are analgesic when administered centrally (Jones and Dunlop, 2007). Muscarinic receptor agonists such as vendacycline, oxotremorine, CMI-936 and CMI-1145, have also shown potent analgesic action (Tata, 2008; Wess *et al.*, 2007). Furthermore, neostigmine, which inhibits the degradation of acetylcholine, reversed allodynia and hyperalgesia in rat models of neuropathic pain (Jones and Dunlop, 2007). As is the case for GABA, specific cholinergic receptor subtypes may be important in the interaction between pain and cognition. A recently characterised partial agonist of the nicotinic acetylcholine receptor $\alpha 7$ subtype, JN403, was found to have antinociceptive effects in rats and improved social learning in a social recognition paradigm (Feuerbach *et al.*, 2008). Thus, the cholinergic system may subserve pain/cognition interactions.

The endocannabinoid system is involved both in pain (Graham *et al.*, 2009; Hohmann and Suplita, 2006) and in the cognitive processes of learning and memory (Riedel and Davies, 2005; Solowij and Battisti, 2008). Inflammatory and neuropathic pain were found to be associated with increased levels of endocannabinoids in the rat PAG (Petrosino *et al.*, 2007; Walker *et al.*, 1999), and PAG cannabinoid CB₁ receptor expression was increased in a rat model of diabetic hyperalgesia (Mohammadi-Farani *et al.*, 2010). In the ACC,

endocannabinoid levels and cannabinoid CB₁ receptor expression were unchanged in the mouse CCI model of neuropathic pain, but receptor coupling/functionality (measured by [³⁵S]GTPγS binding) was decreased (Hoot *et al.* 2010). Therefore, pain is associated with region-specific alterations in endocannabinoid signalling in brain regions associated with cognitive processing. Cannabinoid receptor agonists are associated with impaired performance in spatial learning and recognition memory tasks (Ferrari *et al.*, 1999; Kosiorek *et al.*, 2003; Suenaga and Ishitani, 2008; Suenaga *et al.*, 2008; Takahashi *et al.*, 2005), while cannabinoid receptor antagonists improve performance in cognitive tests (Lichtman, 2000; Wise *et al.*, 2008; de Bruin *et al.*, 2010). Cannabinoid ligands have also demonstrated antinociceptive effects in acute, inflammatory and neuropathic pain models (Finn and Chapman, 2004; Manzanares *et al.*, 2006), and have a synergistic analgesic effect when co-administered with opioids (Welch and Eads, 1999). However, there is a paucity of studies directly investigating potential involvement of the endocannabinoid system in pain-related cognitive impairment.

N-acetyl aspartate is a precursor of the excitatory neurotransmitter aspartate and is known to be localized to neurons involved in synaptic processes. Reduced levels of this molecule were found in the PFC of patients with chronic lower back pain (Grachev *et al.*, 2000). Attentional interference in the Stroop task is associated with reduced N-acetyl aspartate in the ACC (Grachev *et al.*, 2001). Decreased N-acetyl aspartate occurs in a number of degenerative disorders, and is thought to be indicative of neuronal loss. These changes in cortical organisation may again contribute to impairments in cognitive functioning. Grachev *et al.* (2000) also found reductions in glucose in the PFC of chronic pain patients, which may suggest a decrease in metabolic rate in this region, which in turn might be expected to affect performance on cognitive tests.

The neurotransmitter systems discussed above are potentially altered in chronic pain by increased or decreased activation, or by disinhibition. As these systems are also crucial to normal cognitive functioning, alterations caused by chronic pain may negatively affect cognition. Further research is needed to confirm this hypothesis, and to fully investigate the relative contribution of each system and the interaction between them.

5.3 Glial cells and cytokines in pain and cognition

Chronic pain is also associated with changes in neural mediators other than classical neurotransmitters. These include cytokines, glial cells, enzymes and neurotrophic factors. Dysregulation of these mediators could also affect cognitive processing ability.

Recent research has highlighted the importance of glial cells in relation to pain (Inoue and Tsuda, 2009; McMahon *et al.*, 2005; Miller *et al.*, 2009), and in processes such as synaptic plasticity, important for learning and memory (Bains and Oliet, 2007). Furthermore, activated glial cells can release a variety of cytokines and neurotrophic factors which also modulate neural processes involved in pain and cognition (Covey *et al.*, 2000; Ren and Dubner, 2008; Tanaka *et al.*, 2006). The SNL model of neuropathic pain in mice is associated with increased activation of astroglia in the ACC (Kuzumaki *et al.*, 2007), a region which, as discussed previously, plays a vital role in pain and cognition. In addition, administration of the glial modulating drug, propentofylline, directly into the cingulate cortex 24 hours before ligation had anti-allodynic and anti-hyperalgesic effects (Kuzumaki *et al.*, 2007). A role for glial cells in chronic pain and associated mental fatigue has been proposed by Hansson and Ronnback (2004). These authors suggest that pro-inflammatory cytokines, released by activated microglia, cause impaired uptake of the neurotransmitter glutamate by astroglia. This leads to an accumulation of glutamate in the extracellular space which in turn diminishes synaptic efficiency, reduces the precision of glutamate signalling, and eventually

reduces stimulus-induced glutamate release. One may speculate that these changes might underlie poor cognitive performance in chronic pain, though further research is necessary to confirm this theory. Cytokines are signalling molecules expressed in most pain states, but are most classically associated with inflammation. Cytokines are now also thought to be involved in synaptic plasticity and memory consolidation (Depino *et al.*, 2004). Levels of pro-inflammatory cytokines, IL-1 β and IL-6, are increased in the CSF of chronic pain patients (Alexander *et al.*, 2005). In the rat SNI model of chronic neuropathic pain, levels of the pro-inflammatory cytokine, IL-1 β , were elevated in the brainstem and in the right PFC at 10 days post-injury (Apkarian *et al.*, 2006). Pain-induced changes in cytokine expression in brain regions such as the PFC may, therefore, affect cognitive functioning by altering synaptic processes.

5.4 Enzymes in pain and cognition

The enzyme calcium (Ca²⁺)/calmodulin-dependent kinase II (CAMKII) is an interesting molecule in the context of pain/cognition interaction. Over-expression of forebrain (ACC, hippocampus and amygdala) CAMKII in transgenic mice is associated with antinociceptive effects and decreased long term depression (LTD) in the ACC (Wei *et al.*, 2006). LTD, or weakening of synaptic efficiency, is induced by a low-frequency prolonged stimulation, and is considered to be the reverse of LTP. It is thought to be involved in erasing old memories and allowing the formation of new memories. Therefore impaired LTD in the ACC may inhibit the removal of pain-related memories. However, it is important to note that since LTD weakens synaptic efficiency, inhibition of this process may in fact facilitate cognition. In a separate experiment, mutations in the gene encoding CAMKII inhibited LTP in the hippocampus and impaired spatial learning in the water maze (Giese *et al.*, 1998). Thus supraspinal CAMKII appears to be important in both pain and cognition, though its potential role in the interaction between pain and cognition is yet to be investigated directly.

Neuropathic pain was associated with increased expression of caspases in the prefrontal cortex (Neugebauer *et al.*, 2009). Caspases are a family of cysteine protease enzymes and are thought to be involved in regulating the release of cytokines, as well as playing a central role in apoptosis (Thornberry and Lazebnik, 1998). Expression of the effector caspase, caspase 3, may reflect cell death associated with neuropathic pain in the prefrontal cortex, which could contribute to cognitive dysfunction (Neugebauer *et al.*, 2009).

5.5 Neurotrophic factors in pain and cognition

BDNF plays a critical role in synaptic plasticity, memory processes and storage of long-term memory (Bekinschtein *et al.*, 2008a; Bekinschtein *et al.*, 2008b; Yamada and Nabeshima, 2003). BDNF has also been found to enhance neurogenesis (Binder and Scharfman, 2004), thought to be important for hippocampal-dependent learning and memory. BDNF expression in the hippocampus was decreased in models of both neuropathic pain and inflammatory pain (Duric and McCarron, 2006; Hu *et al.*, 2010). Moreover, pharmacological alleviation of neuropathic pain-related behaviour was associated with increased levels of BDNF and reversal of pain-related cognitive impairment. These findings suggest that pain-induced decreases in BDNF may mediate cognitive impairment.

The literature reviewed above provides support for a model of pain-related cognitive impairment based upon three main theories; (1) limited resources, (2) altered neuroplasticity and (3) dysregulated neurochemistry. Pain utilises cognitive resources, alters neural plasticity and affects expression and activity of a variety of chemical and cellular neuromediators. These effects, which are not necessarily mutually exclusive, occur across a complex network of interconnected cognition-related brain regions to produce a net cognitive impairment. This theoretical model is illustrated in Figure 1. Though the model presented is necessarily

speculative at this time, it may provide a framework for the design of further studies aimed at elucidating the neural mechanisms involved in pain-related cognitive impairment.

6. The effects of analgesic treatments for chronic pain on cognitive function

Treatment of chronic pain represents a major challenge for healthcare professionals.

Multimodal analgesia is often necessary to achieve adequate pain relief. Protracted medical management is often required in patients suffering from chronic pain. Current strategies for the management of pain focus mainly on its sensory component. Pharmacological interventions treat inflammation and associated sensitisation of nociceptors (non-steroidal anti-inflammatory drugs; NSAIDs), enhance endogenous analgesic mechanisms (opioids, tricyclic antidepressants; TCAs) or dampen the excitability of pain transmitting neurons (opioids, anticonvulsants). Some of these agents may be associated with cognitive dysfunction *de novo*, or further exacerbation of existing cognitive impairment.

As illustrated in Table 3, the cognitive profiles associated with analgesic drugs, are complex and varied. Opioid, TCA and anticonvulsant drugs have all been related to impaired cognitive function in various domains (see Table 3), though inconsistently. Other studies have found no adverse cognitive effects with these medications or have actually found improvements in cognitive function, particularly in chronic pain patients and in animal models of chronic pain (Boyette-Davis et al., 2008; Hu et al., 2010; Jamison et al., 2003; Millecamps et al., 2004; Tassain et al., 2003). Proposed explanations for these findings include development of tolerance to the adverse cognitive effects, as well as the idea that effective pain relief reverses pain-induced cognitive impairment. Combined Δ^9 -tetrahydrocannabinol (THC) and cannabidiol was not shown to affect cognition and NSAIDs were found to improve cognition (Table 3).

In assessing cognitive function in chronic pain patients, the majority of studies fail to adequately control for confounds related to analgesic medication. Of the clinical studies outlined in Table 1, only one study controlled fully for the effects of medication by including a non-medicated comparison group as well as drug-treated groups (Sjogren *et al.*, 2005). These authors found that patients taking oral opioids performed more poorly than the non-medicated group on the PASAT (which measures attention, concentration, working memory and speed of information processing). Patients in another study were free of any medication (Povedano *et al.*, 2007). Some studies were performed following a drug wash-out period (Antepohl *et al.*, 2003; Park *et al.*, 2001). In some cases authors excluded patients taking opioid or antidepressant drugs (Harman and Ruyak, 2005) or corrected statistically for the effects of medication status (Eccleston, 1995; Karp *et al.*, 2006; Lee *et al.*, 2010; Oosterman *et al.*, 2010). The inclusion of non-medicated control groups may not always be possible in studies involving chronic pain patients for ethical reasons. However, many analgesic drugs are known to affect cognition and this property could alter or confound the results of neuropsychological assessment in chronic pain patients.

Cognitive impairment associated with analgesic medication may, therefore, further exacerbate pain-related cognitive impairment, but effective analgesia may alleviate pain and its associated cognitive impairment. Examining the effects of analgesics on cognition and pain-related cognitive impairment may also help to elucidate the mechanisms underlying cognitive impairment in chronic pain. Analgesic reversal of pain-related cognitive impairment, as occurs with opioids and amitriptyline (Boyette-Davis *et al.*, 2008; Hu *et al.*, 2010; Jamison *et al.*, 2003; Millecamps *et al.*, 2004; Tassain *et al.*, 2003), is an important factor in defining a causal relationship between chronic pain and cognitive impairment. Future research should examine whether similar effects occur with other classes of analgesic drugs.

7. Conclusions and future directions

There appears to be sufficient evidence from preclinical and clinical investigations to support the theory that pain is associated with impaired cognitive function. Cognitive deficits in tests with high ethological validity, suggest that cognitive impairment in pain patients may be an obstacle to everyday tasks. As such, this impairment may have a marked impact on patients' quality of life. There is also some evidence for a mechanistic, neuropathological basis for pain-related cognitive impairment. Given the considerable overlap that exists between the neuroanatomical and neurochemical substrates implicated in both pain and cognition, and studies demonstrating pain-related alterations at cognitive behavioural, morphological, neurochemical and molecular levels, we have proposed a model to explain the potential mechanisms involved in pain-related cognitive impairment (Figure 1). This model is based on the three theories of (1) competing limited resources, (2) neuroplasticity and (3) dysregulated neurochemistry. It is hoped that this model and literature review will provide a useful framework to inform future research aimed at further elucidating the precise causal mechanisms that mediate pain-related cognitive impairment. The utility of pre-clinical animal models, sophisticated neuroimaging techniques, and translational research approaches will be important in this process. Identification of the precise mechanisms involved in pain-related cognitive impairment, and due consideration of the effects of analgesic drug treatment on cognition, may allow development of novel interventions to reduce cognitive deficits. Overall, a better understanding of pain- and treatment-related cognitive dysfunction should help to improve treatment outcomes in chronic pain patients.

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Figure legend

Figure 1: Potential mechanisms of pain-related cognitive impairment, a theoretical model. Pain-induced changes in resource utilisation, neuromediators and neuroplasticity may affect cognition through a network of brain regions. PFC: prefrontal cortex, IC: insular cortex, Hipp: hippocampus, Amy: amygdala, PAG: periaqueductal grey, ACC: anterior cingulate cortex, LTP: long-term potentiation, EPSP: excitatory post-synaptic potential, BDNF: brain-derived neurotrophic factor, ECs: Endocannabinoids