Published in final edited form as:

Pain. 2015 April ; 156(0 1): S42–S49. doi:10.1097/01.j.pain.0000460347.77341.bd.

Effect of environment on the long-term consequences of chronic pain

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Abstract

Much evidence from pain patients and animal models shows that chronic pain does not exist in a vacuum, but has varied co-morbidities and far-reaching consequences. Patients with long-term pain often develop anxiety and depression and can manifest changes in cognitive functioning, particularly with working memory. Longitudinal studies in rodent models also show the development of anxiety-like behavior and cognitive changes weeks to months after an injury causing long-term pain. Brain imaging studies in pain patients and rodent models find that chronic pain is associated with anatomical and functional alterations in the brain. Nevertheless, studies in humans reveal that life-style choices, such as the practice of meditation or yoga, can reduce pain perception and have the opposite effect on the brain as does chronic pain. In rodent models, studies show that physical activity and a socially enriched environment reduce pain behavior and normalize brain function. Together, these studies suggest that the burden of chronic pain can be reduced by non-pharmacological interventions.

1. Introduction

There is accumulating evidence that chronic pain leads to consequences that go far beyond the pain itself. Chronic pain patients show associated anxiety and depression, as well as deficits in cognitive functioning [101; 106]. Rodent models confirm similar emotional and cognitive changes in controlled longitudinal studies [85; 135], suggesting that at least some of the comorbidities may be caused by the chronic pain condition, rather than reflecting unrelated differences between individuals with chronic pain and control subjects. Brain imaging studies in both pain patients and in rodent pain models show alterations in gray matter volume, white matter integrity and even epigenetic changes in the brain[17; 144]. Despite the widespread nature of the alterations related to chronic pain, there is now evidence suggesting that these effects may possibly be prevented or reversed by environmental factors. In human pain patients, lifestyle choices, such as yoga or meditation, have been shown to reduce pain perception and may counter age-related decreases in gray matter density and improve white matter integrity [49; 155]. This contrasts with chronic pain

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No author has any conflict of interest to declare.

that sometimes accelerates gray matter loss and can disrupt white matter integrity. Rodent models show that increased stress alters pain behaviors, whereas socially and physically enriched environments can reduce such behavior and reduce pain-related brain changes[42]. This review will highlight evidence of the far-reaching adverse effects of chronic pain and present data in humans and animal models indicating that these consequences are not inevitable and may be reduced or prevented by environmental and lifestyle factors (Figure 1).

2. Chronic pain does not exist in a vacuum, but has varied comorbidities

Many long-term chronic pain patient have not only pain, but also have some comorbidities, such as increased anxiety, depression or changes in memory and other cognitive functions. It has been estimated that up to 50% of chronic pain patients suffer co-morbid mood disturbances, including anxiety and depression [7;15; 48; 97; 101]. The presence of such comorbidities has been linked to poor treatment outcomes [6; 76].

In addition to having mood disturbances, many chronic pain patients show difficulties in concentrating and remembering [45; 96; 106; 121; 153]. These cognitive disturbances are confirmed in experimental studies, where chronic pain patients perform poorly on tests of attention and memory, especially in the presence of distraction [13; 33; 34; 36; 47; 55; 82; 83; 105]. There is also some evidence that chronic pain patients show impaired emotional decision-making [3; 154; 157]. Altered mood, such as having depression or anxiety, could impair cognitive functioning, however cognitive impairments in chronic pain patients are evident even after controlling for mood symptoms [34; 45; 83; 99; 121], suggesting a direct effect of ongoing pain on cognitive capacity.

3. Pain co-morbidities in rodents: increased anxiety, depression and altered cognition

The co-morbidities seen in human chronic pain patients, such as increased anxiety, depression and changes in cognition, can also been seen in animal models of pain. Animal models allow researchers to determine the correlative or causative effects of a pain model or treatment, and can allow the neurobiological bases of these changes to be investigated in a way that is not possible in human studies.

The literature examining co-morbidities in animals, particularly rodents, has expanded dramatically in the last decade, and now proof of a comorbid condition (or reduction thereof via a treatment) is rapidly becoming a 'gold standard' to show that pain is having an emotional, affective component in addition to a sensory component.

Anxiety-like behavior is often modeled in animals using tasks that monitor the time a rodent spends in a section of an arena. Using an open field box, investigators can monitor the degree of thigmotaxis (wall-hugging) that a rodent shows, and equipment such as the elevated plus and elevated zero mazes consist of exposed and sheltered raised platforms. Open spaces and elevated/exposed platforms are naturally anxiogenic for rodents, so that they will spend the majority of their time around the walls or in the sheltered sections.

However, anxiolytics increase the time spent in the center/on an exposed section, which is posited to be a reflection of a reduction in anxiety [31]. In the pain literature, multiple studies have demonstrated an increase in anxiety-like behavior that develops over the course of a few weeks, as seen using the open field, elevated plus maze and elevated zero maze in nerve injury [84; 131; 135; 143] and inflammatory pain models [120]. In addition, administration of an analgesic drug can increase the amount of time spent in exposed areas, i.e. showing a decrease in anxiety-like behavior [95; 109; 156].

Depression is another comorbidity in humans that can be seen in rodent pain models. It is often measured using the forced swim test or the tail suspension test. The outcome measure for both of these is the amount of time the rodent spends immobile, i.e. not swimming or struggling – a proposed measure of ‘behavioral despair’ that decreases when animals are administered anti-depressants [31]. Multiple laboratories have shown that chronic pain increase the amount of immobility in these tests [2; 46; 84; 111; 160], and researchers have concluded that pain increases depression-like behaviors in rodents, and that successful analgesia can reduce this behavior [39; 127]. However, two important points to note when interpreting these results are that the tests are inherently stressful (which can impact behavioral responses), and that animals in pain, particularly those with nerve injuries, may have mobility issues, which will confound behavioral readouts [160]. Non-motor behavioral monitoring, such as sucrose preference (an animal model of anhedonia) is seen to shift in chronically injured rodents, and may be more appropriate for some pain models [107; 158].

As pain can interrupt cognitive processes in humans, so researchers have seen similar interruptions in rodents. While rats and mice cannot be equated to humans in terms of their cognitive abilities, they can still perform a variety of ‘executive functions’ such as decision-making, memory and attention tasks, and recognition of objects, just like humans. In addition, these tasks rely on analogous prefrontal cortical areas [27]. Pain has been shown to interrupt working memory tasks in rodents, where rats or mice must remember where they searched for, or poked their noses for, a food treat or a dry platform in a water pool [19; 20; 66; 84; 127]. Tasks that rely on attending to the surroundings are also interrupted by acute [14; 100] and chronic [86; 118] pain states, as are object recognition tasks [37; 73]. Even complex mental computations of probability of reward, which can be calculated by uninjured animals, are interrupted by pain states [68; 117; 119].

While rodent research can be a useful adjunct to human studies, it must be performed carefully, as behavioral research is particularly vulnerable to influence by non-experimental factors. Differences in protocols, measurements and laboratory procedures can lead to wide variability in results, or no effect seen at all [61; 73]. In addition, data must be interpreted in terms of the animals’ normal behavioral repertoire and anthropomorphism should be avoided. Home cage behavioral monitoring can identify changes in ‘normal’ rodent behavior induced by pain, but a recent paper showed no differences in affective state between injured and uninjured mice, of a variety of strains and pain models, over the course of weeks of monitoring and behavioral testing, suggesting that there is still the need for development and validation of rodent models of ‘lifestyle changes’ [150]. In addition, the overwhelming majority of rodent research has been done in males, despite the clinical evidence that females are more likely to suffer from pain states. Development of these kinds of ‘Quality of

life' models and tests in both genders would make rodent research more translatable to humans [103].

4. Chronic pain affects the brain

Structural magnetic resonance imaging (MRI) studies in multiple types of chronic pain patients show that the brains of these individuals differ from those of matched healthy control subjects. The most pronounced abnormality observed across studies is a reduction of gray matter in patients, most consistently in the prefrontal cortex, insula, and anterior and mid-cingulate cortices (ACC, MCC) (as reviewed in [17; 32]. These are brain regions implicated in pain processing and regulation, mood regulation, and cognition. Brain regions having more gray matter in chronic pain patients than in controls have also been reported. These increases have frequently appeared in younger pain patient groups, so that it has been suggested the gray matter increases could be a precursor to later gray matter decreases ([23; 132] [102]. Nevertheless, other factors, such as the presence or absence of sensory loss in addition to pain, could contribute to whether or not gray matter changes are predominantly loss or gain.

One problem with interpreting the brain morphological differences between pain patients and healthy individuals is the cross-sectional nature of the studies. Are the brain differences cause or effect of the chronic pain? By correlating pain duration with the brain anatomy, we can begin to answer this question—if the gray matter differences correlate with the duration of symptoms, it is likely that the pain is at least a partial causative factor. Studies that have examined this relationship have in fact found that gray matter decreases in chronic pain patients correlate with the duration of pain symptoms [4; 44; 77; 114; 129] suggesting that prolonged pain may contribute to the reduced gray matter. Several other studies have been able to examine the brains of long suffering patients with back pain or arthritis who eventually received relief through surgery [136] [57; 130]. These studies found at least a partial normalization of brain morphology within months of the effective treatment, further suggesting that the pain contributes to the anatomical abnormalities.

A more definitive way to examine cause and effect between chronic pain and brain anatomy is to perform longitudinal studies in animal models of chronic pain. With these models, genetic and environmental factors can be controlled, while animals showing chronic nociceptive behavior are compared to sham controls. Rats and mice, with short lifespans can be examined across several months, which is equivalent to decades of a human lifespan. Seminowicz et al [135] compared rats that had received a partial nerve injury (spared nerve injury—SNI) to sham-operated controls and found that approximately five months post-injury the brains of the injured rats showed gray matter decreases in the frontal and somatosensory cortices, some of which correlated with the magnitude of pain behavior.

5. Contribution of pain co-morbidities to brain abnormalities

Several studies have examined the relationship between pain comorbidities and brain changes and found that the amount of depression or anxiety in the pain patient correlates with decreases in gray matter in at least some brain regions, [56; 65; 91; 134]. Similarly,

Seminowicz et al [135] found that rats began to develop anxiety-like behavior at approximately the same time as gray matter decreases were observed in the frontal cortex.

There is also some evidence that the magnitude of cognitive dysfunction in chronic pain patients correlates with reduced gray matter in frontal and cingulate cortices, regions important for memory and attention [89]. Similarly, rats manifest signs of reduced memory function several months after an SNI injury [86] at a time point consistent with the reduction in gray matter observed by Seminowicz et al [135].

6. Mind-body practices can alter pain and pain-related co-morbidities

In contrast to the many negative consequences of chronic pain, there is now considerable evidence that certain mind-body practices can have multiple positive effects on pain and its consequences. Studies of yoga- and mindfulness-based interventions of varying length, including randomized control trials, suggest that these mind-body techniques can be useful to alleviate various painful conditions and reduce pain-related comorbidities, including depression, anxiety and fatigue (reviewed by [18; 26; 124; 126; 159]. Additionally, several studies show that experimentally induced pain is decreased in both experienced and novice practitioners of mind-body techniques. When compared to controls, experienced meditators from Vipassana and other Buddhist-based traditions reported reduced pain unpleasantness ratings in response to various nociceptive stimuli during meditative states, while pain intensity ratings were unaffected [43; 90; 122]. However, one group repeatedly found decreased pain sensitivity in experienced Zen meditators relative to controls, both during and outside meditative states, with meditators requiring higher temperatures to report a moderate level of pain intensity [49–51]. Experienced yoga practitioners of various traditions showed increased cold pain tolerance, a measure mainly determined by the affective dimension of pain [125], compared to healthy controls not practicing any type of mind-body techniques [155]. Even short-term mindfulness interventions have led to improved cold pain tolerance when not meditating [72] and reduced pain ratings associated with brief electrical pulse during meditation [161]. Together these studies suggest that mind-body techniques can be used in the management of chronic pain conditions. They apparently decrease both the sensory-discriminative and affective-motivational aspects of pain even while not actively engaged in the practice.

7. Mind-body practices have the opposite effect on the brain as chronic pain

In contrast to the observations in chronic pain patients of increased age-related gray matter decline [23; 77], mind-body practices appear to counter normal age-related decrease in gray matter volume [116]. Furthermore, the practice of mind-body techniques such as yoga and meditation is associated with more gray matter volume or cortical thickness in numerous brain regions including primary and secondary somatosensory cortices, insula, anterior and posterior cingulate cortices, superior and inferior parietal cortices, hippocampus, medial prefrontal and orbitofrontal cortices [38; 49; 62; 63; 80; 88; 155]. These brain regions are involved in pain perception, pain modulation, attention, interoceptive awareness, autonomic control, and emotional regulation. Further, hypertrophy in at least some of these structures

has been shown to correlate with yoga or meditation experience, suggesting that these structural differences may be the result of use-dependent neuroplastic changes [38; 49; 63; 80; 155]. Importantly, changes in pain perception are associated with structural differences in some of these regions in mind-body practitioners. Increased insular volume or thickness correlated with both increased pain tolerance [155] and decreased pain sensitivity [49]. Additionally, lower pain sensitivity was associated with thicker anterior cingulate and parahippocampal cortices [49]. Structural changes in these three brain areas, especially the anterior cingulate and insula, are often described in various chronic pain conditions (reviewed by [12; 17]).

Experienced meditators were also found to have greater white matter connectivity than controls throughout the entire brain [87] in contrast to chronic pain, which can disrupt white matter connectivity [23]. Even a short-term meditation intervention has been shown to induce changes in the corona radiata, a white matter tract connecting the anterior cingulate cortex to other brain structures [146]. Additionally, experienced yoga practitioners had higher fractional anisotropy than controls in white matter adjacent to the left posterior insula and connecting this region with the anterior portion of the insula, suggesting enhanced intra-insular white matter connectivity in yogis [155]. In summary, these psychophysiological and neuroanatomical findings suggest that the practice of mind-body techniques such as yoga and meditation could potentially counteract some of the negative consequences associated with chronic pain conditions.

8. Physical and social environment affects chronic pain in humans

Important components of mind-body practices include exercise and social interactions. Some studies have addressed these directly and found that each is important for the development and maintenance of chronic pain. Meta-analysis of clinical studies demonstrates a large positive effect of psychological interventions on chronic pain in pediatric patients [69]. Cognitive-behavioral therapy, relaxation therapy, and biofeedback all reduce pain in these patients, likely through reduction of stress, anxiety, and depression. Social support is associated with lower levels of chronic pain, labor pain, cardiac pain, and postoperative pain [92] and also reduces perception of induced pain in controlled experimental settings [16]. Exercise is also often helpful for patients with chronic pain, although the mechanism of pain reduction is unclear. Recreational activity is negatively associated with chronic pain in the general population [79], and exercise has been found to reduce pain in a number of chronic pain conditions including fibromyalgia, chronic neck pain, osteoarthritis, rheumatoid arthritis, and chronic low back pain [110].

9. Physical and social environment affects chronic pain in rodents

As discussed above, rodent models of persistent inflammatory or neuropathic pain mirror many aspects of chronic pain in humans, both in terms of hypersensitivity and the presence of comorbidities such as anxiety, depression and cognitive deficit. Similarly, adjunct treatment approaches such as increased physical activity and social interaction improve outcomes in rodents, as they do in humans. In rodent studies, the term environmental enrichment collectively applies to social enrichment (i.e. more cagemates) and physical

enrichment (i.e. access to exercise, larger cage size, additional nesting material/toys) [149]. A number of studies have shown that environmental enrichment is effective in attenuating persistent hypersensitivity in inflammatory [40–42; 145], neuropathic [9; 144; 151] and postoperative [123] pain states. Putative pathways underlying these beneficial effects include altered glial cell activation [40; 42], reduced spinal BDNF [9] and neuropeptide signaling [151], as well as epigenetic mechanisms [144].

In terms of the pain-related co-morbidities observed in humans, such as anxiety, depression and cognitive decline, rodent studies have found that environmental enrichment increases cognitive function and reduces baseline anxiety- and depression-like behavior in healthy rodents (Reviewed in [60; 140]). Nevertheless, the few studies that have attempted to measure these outcomes in persistent pain states did not observe meaningful effects [42; 151].

Just as mind-body practices in humans have multiple features, including physical activity, emotional regulation and cognitive stimulation, environmental enrichment in rodents can consist of multiple components, including exercise, cognitive stimulation and social interaction. However, rodent models allow us to separate these components and examine how each contributes to the positive effects of the enriched lifestyle on pain. Studies examining specifically the effects of physical exercise on nociceptive behavior in rodents show that exercise can be effective in attenuating persistent hypersensitivity following both inflammatory and neuropathic injury. Nevertheless, most of the studies of exercise in rodents use forced exercise on a treadmill. This reliably produces analgesic effects in rats and mice [8; 10; 24; 25; 28; 29; 67; 75; 137; 138; 142] that appear to act through endogenous opioidergic mechanisms [137; 142]. Much less studied is voluntary exercise, in which the animals are given access to a running wheel or other exercise equipment, and are allowed to use it as much or as little as desired. Voluntary exercise has also been shown to reduce nociceptive behavior in mice that had access to running wheels in their home cages [141]. Nevertheless, although mice readily run when provided a wheel, the amount of voluntary running in rats is highly variable [1], leading to the widespread use of forced exercise for mechanistic studies. However, forced exercise is highly stressful [30; 54; 70; 81; 104; 108], thus confounding the analgesic effects of exercise with the known analgesic effects of stress [115]. Similar to forced running, forced swimming effectively reduces persistent hypersensitivity [67; 139]; however, it too has long been considered a potent stressor producing opioid-dependent stress-induced analgesia [11; 21; 113; 147; 148]. Therefore, the opioid-dependent analgesic effects of forced exercise paradigms may be due at least in part to stress. In contrast, voluntary exercise is less stressful [30; 52; 54; 70; 81; 98; 133] and can in fact be considered rewarding [52; 112]. In healthy rodents, voluntary exercise promotes anxiolytic and anti-depressant effects [35; 53; 133], enhanced cognitive function/neuroprotection [5; 70; 71] and decreased mortality [108]. Yet, to our knowledge no studies have yet addressed potential exercise-induced effects on cognitive and affective disturbances that often occur as co-morbidities in persistent pain states.

Chronic pain patients often are socially isolated, because their pain interferes with their ability to work or engage in social activities. As discussed above, such isolation in chronic pain patients is thought to have a negative impact on treatment outcomes [22]. In rodents,

social isolation is widely accepted to be highly stressful, as it is in humans [64]. As such, even in physically enriched conditions social isolation can result in poorer pain outcomes in rodent studies [123]. On the other hand, while social enrichment improves pain outcomes compared to a socially impoverished group, it is somewhat less effective than physical enrichment [42]. In fact, co-housing multiple rodents in large, complex cages may actually increase aggressive behavior through production of unstable social dominance hierarchies [58; 59; 78; 93; 152], potentially altering measures of hypersensitivity. Accordingly, social defeat stress, a particularly powerful social stressor in rodents [74], can significantly alter sensory hypersensitivity and anxiety-like behavior [94; 128]. Therefore, while social isolation is highly stressful, establishment of a stable dominance hierarchy is critical for effectively studying the influence of social enrichment on chronic pain in rodents.

There is a growing interest in non-pharmacological approaches to control chronic pain and common comorbidities such as anxiety and depression. While rodent studies have demonstrated that exercise and social interaction can be beneficial in models of persistent pain, few studies have assessed how these approaches alter affective processing. Moreover, inappropriate application of these enrichment strategies may in fact increase stress, potentially confounding results. Therefore, while promising, rodent enrichment strategies require careful implementation to render meaningful results.

10. Conclusions

For many chronic pain sufferers, pain is only one aspect of their burden. Co-morbid mood and cognitive disturbances are common and result in poorer treatment outcomes. Studies of pain in rodent models also document heightened anxiety and depression-like behaviors and cognitive disturbances that may be caused by the chronic pain. Indeed, many animal models of pain now include measures of affective disturbance, and the affective symptoms are often reduced by analgesic treatment.

Chronic pain may also change the brain. Some patients with chronic pain show accelerated loss of gray matter relative to healthy controls. This loss is correlated with duration of chronic pain and often normalizes with treatment, pointing to pain as a possible cause of gray matter decline. Similar gray matter decline has been observed in longitudinal rodent models of chronic pain, further suggesting that chronic pain leads to brain changes. In both rats and humans, correlations have been observed between the time course of gray matter loss and mood and cognitive disturbances, suggesting that brain changes may contribute to some of the affective and cognitive co-morbidities of chronic pain.

Despite these far-reaching effects of pain, chronic pain sufferers may take hope in the possible ameliorative effects of environmental and lifestyle factors. Indeed, research on stress, meditation, yoga, and social and physical enrichment suggests that a variety of activities can sometimes counter the effects of pain on the brain and reduce the severity of affective and cognitive symptoms. Mind-body practices like yoga and meditation, for example, alleviate pain and reduce fatigue and affective comorbidities, even in beginning practitioners. Of particular note, mind-body practices appear to exert a protective effect on

the brain gray and white matter that could counteract the negative neuroanatomical effects of chronic pain.

Lifestyle factors related to social life and physical environment also influence the impact of chronic pain in human patients. Animal models replicate these observations in rodents, where physical environmental enrichment can reduce pain hypersensitivity. Healthy rodents also show benefits of exercise on affective symptoms, though more research is needed to determine the affective benefits of physical environment in chronic pain models. Similarly, stress and social isolation cause poor pain outcomes in pain patients and rodent pain models, while social enrichment improves outcome. The demonstration of positive effects of exercise, stress-reduction, and social support in both chronic pain patients and in animal models of chronic pain offers chronic pain sufferers and caregivers new hope for reducing the broad burdens of chronic pain.

Acknowledgments

All authors are supported by the National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda, MD USA.

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Figure 1.

Depiction of the adverse effects associated with chronic pain and how environmental and life-style factors alter pain and its comorbid factors. Chronic pain is associated with anxiety, depression, cognitive dysfunction and changes in the brain. Stress and negative mood can exacerbate chronic pain, whereas positive mood, cognitive-behavioral therapies, exercise, social support, and mind-body and relaxation techniques can reduce the impact of chronic pain.