Associative memory for movement-evoked chronic back pain and its extinction with musculoskeletal physiotherapy

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Chronic, non-specific, low back pain is a disabling, costly, poorly understood and treated clinical problem. The failure of earlier structure-based mechanisms to explain its cause or guide successful treatment, along with the identification of a large psychosocial component, led to the recommendation that it best be managed using a cognitive-behavioural approach. As a result, typical conservative treatment includes a combination of ‘advice’ and an exercise-based intervention such as musculoskeletal physiotherapy. However, recent proposals notwithstanding, both the mechanism(s) for (chronic) pain, as well as response to this type of intervention, remain unclear. The following review presents the hypothesis that, with at least some cases, mechanically evoked symptoms and signs of chronic non-specific low back pain are the product of a sustained associatively learned memory for pain and its behavioural responses. With susceptible individuals, this memory is being inappropriately reinforced by both cognitive emotional factors, and pain-associated proprioceptive (not inflammatory nociceptive) afferent input continually generated in the periphery. Together, the verbal and physical strategies employed by musculoskeletal physiotherapy are proposed to be capable of extinguishing the associatively learned pain memory. They do so by effectively changing ‘top-down’ (cognitive-emotional) and ‘bottom-up’ (afferent input) sources of reinforcement. Extinction is, therefore, likely to be a neurological mechanism underlying the clinical efficacy of this type of intervention.

Keywords: Non-specific back pain, associative learning, memory, extinction, desensitisation, musculoskeletal physiotherapy

Introduction
An understanding of the scientific mechanisms behind clinical observations is a cornerstone of orthodox health care. Recently, mechanisms inferred from responses to static and dynamic movements have been used to classify patients with chronically disabling non-specific low back pain (CDNSLBP). Though comparatively uncommon, CDNSLBP is a costly syndrome frequently referred for treatment with a modern system of therapeutic active and passive movements known as musculoskeletal physiotherapy (MP).

CDNSLBP – the SAB Model
Only a small proportion of people with back pain go on to become chronically disabled. Even so, CDNSLBP, a relatively modern healthcare problem, is of concern for two main reasons. One is that these patients account for the bulk of the now enormous cost for this seemingly ‘benign’ (and mostly self-limiting) symptom. The other, as the title denotes, is that the mechanism(s) responsible for CDNSLBP has proved very difficult to uncover. It is reasonable to assume that greater insight into mechanism(s) would facilitate more effective treatment of this poorly understood and managed clinical condition. Such
knowledge might also lead to strategies that help improve, if not totally prevent, this situation.

The lesson of the 20th century healthcare ‘epidemic’ of back pain was to abandon the original structural-anatomical-biomechanical (SAB) models which were considered to explain the basis of CDNSLBP.5,6 These models comprised simplistic conceptualisations involving deterioration and displacement of intervertebral discs, and segmental hypermobility/hypomobility. False positives and structural/degenerative inconsistencies were, however, repeatedly revealed on MRI, when comparing ‘cases’ with pain-free individuals. Moreover, costly invasive interventions that they inspired frequently failed.7 Popular, non-invasive, passive interventions based on SAB models also failed to satisfactorily manage CDNSLBP or to alter its incidence. Together, this (purely SAB) approach may have served to actually worsen the problem.8

On the other hand, replacing these concepts with the diagnosis ‘non-specific’ is clearly less than satisfactory for all concerned. It has meant that some eight out of ten episodes of back pain are deemed to lack any identifiable ‘organic’ basis. Moreover, the label ‘non-specific’ tends to be misleading. Among other things, it implies that the pain itself has no conventionally known cause or basis. This perception has been compounded by irrefutable evidence that CDNSLBP is heavily influenced by psychosocial factors.9

Despite past experience and subsequent evidence, there remains an ingrained reluctance to discard totally the SAB-type hypotheses for CDNSLBP. Thus, validation is currently being sought for a motion segment ‘instability’ model that revolves around pain-induced muscular insufficiency with continuing vulnerability to tissue ‘injury’.2,10,11 However, demonstrable soundness along with in vivo verification of the model’s basic premise, have been seriously questioned.12 So have certain key elements arising from its adaptation to the ‘diagnosis’ and treatment of CDNSLBP by the physiotherapy profession.13 The general feeling is that, while the theory is intuitively appealing, a number of critical issues still require clarification and verification.13,14 Klaber Moffett and Mannion15 assert that, as currently being offered in physiotherapy circles, the approach needs ‘substantially more investigation in a wider range of settings’. Evidence to date does point to some potential for this intervention to limit episodic recurrence, or ‘relapse’, of back pain.15

It is also necessary to reconcile the concept of chronic pain, structural impairment, disability and biomechanical vulnerability to repeated injury (hence ‘damage’) with a substantial body of contradictory evidence including that recently obtained by Carragee and colleagues. Longer term investigations of patients with degenerative changes (n = 200, for 5 years with 6-monthly assessments) found no correlation between baseline or new spinal ‘abnormalities’ (MRI) and the onset of ‘serious’ back pain and disability (VAS > 6/10, absenteeism).16,17 Moreover, the studies showed that repeated minor trauma did not constitute a risk factor for subsequent serious (chronic) pain or disability.18 As previously demonstrated, chronic non-specific back pain frequently occurred in a setting of compensation and a recognised group of psychosocial factors.9,16,18

Proposal – the associatively learned pain memory hypothesis

These points, together with other evidence, make it desirable to offer alternative explanations for the ‘diagnosis’ and successful management of CDNSLBP with MP. The present proposal is based on evidence that ‘central sensitisation’ for pain shares similar mechanisms with those for (associative) learning and memory.19,20 Also, these mechanisms are known to be involved in the creation of aversely acquired pain memories.21–23 It is proposed that aversely acquired, long-term, pain memory manifests as behavioural responses which have been ‘diagnosed’ and classified by MP as movement-evoked non-specific chronic low back pain (see O’Sullivan2).

Then, according to learning theory and memory mechanisms, evidence suggesting that features intrinsic to the movement-based intervention, MP, could create an inhibitory form of learning known as extinction. Extinction is an important mechanism underlying (psychological) ‘desensitisation-by-exposure’ protocols for human fear and anxiety disorders.24–26 Desensitisation-by-exposure is also said to be the therapeutic principle behind ‘safe’ graduated mechanical stimulation with passive/active movement-based interventions.27,28 Therefore, the proposal that extinction of behaviours associated with an aversely acquired pain memory is a neurological basis for the successful management of movement-evoked CDNSLBP with MP.

The learning theory evidence comes largely from studies of a recognised experimental model of associative learning and memory known as Pavlovian or classical fear conditioning.21–23 Before
Central sensitisation and pain memory

Central sensitisation has been defined as ‘increased responsiveness of nociceptive neurons in the central nervous system (CNS) to their normal [nociceptive] afferent input’. It is important to emphasise that varying degrees and duration of sensitisation of spinal and supraspinal nociceptive pathway neurones is a common and relatively rapid consequence of peripheral tissue insult. As such, it is not a synonym for either ‘psychosocial’ or ‘chronic’. Nor, with musculoskeletal pain does its evoked, subjectively determined presence necessarily contraindicate treatment with MP.

Central sensitisation occurs following intense peripheral noxious stimuli, tissue injury or nerve damage. Clinically, it contributes to pain ‘hyper-sensitivity’ in skin, muscles, joints and viscera. Central sensitisation has a major role in postoperative, post-traumatic and neuropathic pain. It is said to be dominant with specific syndromes such as migraine, fibromyalgia, gastrointestinal tract and tension-type headache pain. To date, its mechanisms have been most studied in the dorsal horn of the spinal cord. However, central sensitisation-like changes are also observed at several supraspinal sites including the brainstem, thalamus, anterior cingulate cortex, amygdala and neocortex. Central sensitisation manifests as a prolonged reduction in threshold, increase in responsiveness and expansion of the receptive fields of (dorsal horn) nocireceptive neurones. Importantly, these neurones also begin to respond to near and distant ‘weak’ inputs that would have had no effect previously. Together, this heightened, persistent multimodal, and multispatial central nervous system hyper-responsiveness points to an increase in synaptic efficacy. Indeed, evidence indicates that increased homosynaptic and heterosynaptic efficacy observed with central sensitisation has substantial parallels with mechanisms for memory storage and retrieval known to occur at supraspinal sites such as the hippocampus.

Molecular mechanisms

That pain possesses powerful memory-like attributes has long been proposed and makes sense in evolutionary terms. Technical advances have now made it possible to investigate likely mechanisms of ‘pain memory’ down to the molecular level in the (central) nervous system.

Centrally, detailed comparisons between molecular mechanisms for pain and those for a recognised experimental model of learning and memory, hippocampal long-term potentiation (LTP) reveal remarkable similarity, as well as certain differences. For example, both require ‘strong’ presynaptic afferent activity, glutamate binding to postsynaptic a-amino-3-hydroxyl-5-methyl-4-isoxazole propionate (AMPA) and N-methyl-D-aspartate (NMDA) receptors, clearance of the NMDA channel magnesium blockade and the subsequent entry of calcium into the postsynaptic cell. With both, intracellular ‘signalling cascades’ then result in phosphorylation of ‘key’ proteins (receptors, ion channels), facilitate AMPA receptor ‘trafficking’ into the postsynaptic cell membrane, and activate gene transcription factors such as cAMP response element binding protein (CREB). In addition, there is evidence indicating that (variants of) hippocampal mechanisms said to be critical for long-term memory formation and consolidation – namely, an autophosphorylating enzyme (CaMKII) and the synthesis of mRNA along with ‘new’ protein – are also present with central sensitisation. A general view suggests that, if anything, many of the differences from hippocampal LTP would tend to strengthen the learning and memory-like characteristics of ‘central sensitisation’ for pain (see Ji et al.).

As Malenka and Bear point out, the actual mechanisms for LTP come in many forms and subserve all manner of experience-dependent central nervous system ‘plasticity’. Furthermore, there are evidently mechanisms in addition to LTP whereby experience-generated activity can modify central neural circuit structure and subsequent function. The authors conclude that redundancy of mechanism is only to be expected considering the value learning and memory for potentially dangerous events has for survival.

A particularly pertinent example of survival-driven synaptic plasticity and its related behaviours is the experimental model of (associative) learning and memory known as Pavlovian or classical fear conditioning. The prototypical associative memory system, Pavlovian conditioning rapidly encodes memories of aversive events. As such, it is acknowledged ‘fertile ground’ for neuroscientists wishing to investigate mechanisms of learning and memory. Importantly, its ‘unquestionable relevance
to the human condition suggests that this model is a suitable medium for discussion of the present proposal concerning the cause, and management, of movement-evoked CDNSLBP with MP. Namely, that pain and its related motoric behaviours are manifestations of an adversely acquired and regularly mechanically and psychologically reinforced associative pain memory. (As will be discussed, the capacity for informed MP to extinguish this memory is a proposed neurological basis for its clinical efficacy.)

**Associative learning and memory**

There are obvious adaptive advantages in being able to register automatically a lasting connection between simultaneously occurring innocuous, and ‘dangerous’ tissue damaging, events or sensory inputs. Once ‘associated’ in this way, under appropriate circumstances the so-called ‘neutral’ (innocuous) cues can later serve as a warning, prompting avoidance, preparation, protection.\(^{21,39,40,44}\)

Experimentally, the potency of such learned associations can be demonstrated by presenting an animal with, say, an innocuous tone or light stimulus in close conjunction with that of pain (typically in the form of an electric shock). After a few such pairings, measurable pain-generated physiological and motor responses (increased heart rate, respiration rate and blood pressure, hormone release, potentiation of the startle reflex, motionless ‘freezing’) are now able to be elicited by the ‘neutral’ stimulus alone.\(^{21,23}\) Notably, the ability to reproduce these dramatic pain-related responses to a ‘neutral’, normally distinct (e.g. auditory, visual) sensory input has been shown to require very little in the way of training (conditioning). Moreover, once acquired, this association is known to be capable of lasting (be evocable) throughout the course of the animal’s life-time.\(^{45}\)

**Amygdala**

Conventional wisdom still places the amygdala at the ‘hub of the fear (learning and) memory circuit’.\(^{33,35,46,47}\) The amygdala is directly involved in the processing of nociceptive input.\(^{31}\) Along with other structures (e.g. anterior cingulate cortex, insula), it makes a major contribution to the affective aspect of pain.\(^{21,23,30,31,47-50}\) Han et al.\(^{51}\) assert that the relationship between pain and affect is reciprocal, and that the amygdala is a ‘neural substrate’ for its mutual mediation. Nociceptive and neutral stimulus information arriving directly from lamina I spinal cord neurones, and indirectly via the thalamus, widespread areas of the cortex and elsewhere, enter and converge on neurones in the basolateral amygdala complex (BLA).\(^{35}\) Importantly, molecular events and induced changes consistent with LTP are seen in the amygdala following fear conditioning.\(^{49}\) Along with sensitising physiological and anatomical synaptic events mentioned earlier,\(^{19,21,34}\) changes leading to structural remodelling of amygdala nerve cell dendrites and their spines have been observed quite early during fear conditioning trials.\(^{52}\) Indeed, Fanselow and Poulos\(^{3}\) maintain that amygdala LTP is critical for fear conditioning, while Maren\(^{35}\) asserts that there is now ‘an abundance of evidence’ linking amygdala LTP with the acquisition and retention of aversely learned (pain) memories.

The central nucleus of the amygdala (CeA), is the main output structure. It sends projections to various somatomotor and autonomic locations including the brainstem peri-aqueductal grey (PAG: motor responses), lateral hypothalamus (sympathetic excitation) and bed nucleus of stria terminalis (stress hormone release).\(^{21,23,47,48}\) In addition, there are numerous (inter)connections between the amygdala and other sub-cortical and cortical areas. These include the hippocampus and parts of the parietal and entorhinal cortices, as well as frontal neocortical areas that are presumed sites of working memory (‘conscience’) and cognitions (‘mind’).\(^{46-48,53}\)

It is particularly relevant to the present proposal that nerve impulses generated by a normally painless stimulus gain access to neurones in areas of the brain which also process input that is ‘unpleasant’, threatening/frightening and frequently the product of actual or potential tissue damage. Furthermore, that as a result of this association, the nervous system comes to anticipate and fear ‘pain’ evoked by the normally painless (neutral) stimulus. It expresses this by displaying pain-relevant physiological and behavioural responses when such an intrinsically innocuous stimulus is presented in isolation. It should be emphasised that, by this stage, the (evoked) pain-related physiological and behavioural responses need no longer be a direct product of nociception. They may instead be the result of otherwise (non-nociceptively) reinforced molecular mechanisms of associative learning and memory.\(^{33}\)

**Amygdala encoding – fear and ‘danger’**

By definition, at least initially, the associative nature of this change involves the convergent influence of ‘neutral’ and noxious stimulus inputs onto the same amygdala neurones (homo- and heterosynaptic facilitation).\(^{49,54}\) The convergent association of ‘weak’ and strong inputs is thought to be necessary to cause LTP-like increases in their synaptic strength.
Movement-evoked CDNSLBP

It is known that afferent input produced by movement comes from the stimulation of superficial and deep-tissue, large-diameter, peripheral mechanoreceptors (here used interchangeably with proprioceptor unless otherwise specified). This evoked proprioceptive input provides information regarding (trunk) position and movement. It is not normally painful.

The present proposal is that, acutely, innocuous proprioceptive input created by static and dynamic movement (the ‘neutral’ input) becomes associated with that for nociception (inflammatory pain) following their convergence at appropriate neurones in the amygdala. The relevant synapses undergo long-term ‘plastic’ changes (LTP), with enhanced sensitivity to both (the homo- and hetero-synaptic) inputs. The now ‘doubly’ enhanced pain evoked by movement may be accompanied by significant affect. This includes ‘unpleasantness’, fear and an exaggerated sense of danger with strong alerting tendencies for such inputs (hypervigilance).

The amygdala and other processing centres such as the anterior cingulate cortex (ACC), insula and prefrontal cortex are believed to be involved in such a ‘cognitive-emotional’ contribution. As a result of this (potentially) emotion-charged association, large-diameter, mechanoreceptive, afferent input becomes firmly ‘implicated’ in the signalling of movement evoked pain.

Following repair and disappearance of the reinforcing pathological nociceptive component, it is usual for such associative ‘memory traces’ along with their behavioural consequences to decline steadily, and subsequently become ‘extinct’. However, with ‘susceptible’ individuals cognitive-emotional influences are proposed to continue to reinforce, and so help sustain, synaptic sensitivity to the normally innocuous/habitual afferent input. Importantly, further reinforcement comes in the form of (patterns of) pain-associated proprioceptive afferent input generated by dysfunctional postures and movements (e.g. unavoidable activities of daily living, ADL). Together, these mutually sustaining ‘top-down’ and ‘bottom-up’ impulse-generating influences are proposed to reinforce both the synaptic events and their behavioural manifestations. The latter are expressed as the clinical symptoms and signs of movement-evoked (back) pain observed clinically. The result is that (with susceptible individuals) the synaptic changes, along with their ‘diagnosed’ consequences, are proposed to persist well beyond normal tissue healing time.

In fact, it is precisely the ‘reinforcing’ mechanical factors, along with their physical and psychological causes and consequences that MP addresses therapeutically. It will be argued that the effective peripheral target of MP’s clinical strategies is the pattern of afferent input generated from musculoskeletal structures by dysfunctional postures and movements, and the learned association this (proprioceptive) input has with pain. Hence, the successful extinction of memory for evoked CDNSLP with MP is, in part, a consequence of its ability to alter habitual or acquired pain-associated patterns of proprioceptive afferent input.

Extinction

In the experimental situation, extinction training results in the creation of a second (inhibitory) relationship between the ‘neutral’ stimulus and its behavioural consequences. Stated broadly, now instead of signalling pain the innocuous sensory input, say proprioception, learns to signal ‘no pain’ (see, for example, Myers and Davis).

This may be achieved by repeatedly exposing the subject to the innocuous stimulus while ‘withholding’...
the painful one. Sufficient solitary ‘exposure without danger’ of this nature eventually results in disappearance of the previously conditioned response or behaviour.\textsuperscript{24,26,43-60} The premise is that sensory input evoked by the formerly threatening and feared (hence, often avoided) innocuous stimulus, is once again recognised by the nervous system for what it normally is. As a result, it is removed from the repertoire of ‘associated’ inputs that automatically signal ‘danger’.\textsuperscript{38,43,56} However, it should be noted that, while an aversely acquired pain memory now has a functionally relevant ‘mask’ placed over it,\textsuperscript{64} it is not permanently eradicated.\textsuperscript{26,43,56} Under certain circumstances, it is possible for an extinguished associative ‘pain’ memory to re-emerge, along with its behavioural consequences.\textsuperscript{65,66} This fact is important because it constitutes an alternative (addition?) to the acquired muscular insufficiency, ‘injury’ predisposition mechanism for recurrence of back pain proposed recently (see below).\textsuperscript{10} Such structure-based vulnerability has been inferred to lead ultimately to pathological motion segment instability and the development of CDNSLBP.\textsuperscript{2,10,13,15,62}

**Molecular mechanisms**

Since extinction is also a form of learning, it would be expected to share many (although not all) anatomical and molecular mechanisms with different types of learning and memory, including LTP.\textsuperscript{38,67}

Anatomically, cortical and subcortical centres connected with the amygdala, principally the ventromedial prefrontal cortex, appear to be selectively involved in the extinction process.\textsuperscript{68} Within the amygdala itself, recent evidence indicates that, along with that for averesely acquired memories, the BLA is also a parallel inhibitory storage site for their extinction.\textsuperscript{38} A feed-forward circuit capable of inhibiting the principal BLA excitatory neurone has been identified at this location. This pathway would appear to have the ideal situation, and appropriate (inhibitory) synaptic connections, to block excitatory output transmission in the amygdala. As a result, symptoms and signs generated by an associatively learned pain memory are no longer expressed from other identified areas of the brain.\textsuperscript{38}

 Appropriately, synapses in this (presumed) extinction memory pathway have been shown to display LTP. Hence, as with acquisition, extinction requires NMDA receptors, L-type voltage-gated calcium channels, second messenger intracellular signalling cascades (e.g., kinases such as cAMP, PKA, ERK/MAPK group and, notably, phosphatases such as calcineurin), and probably as well ‘new’ protein synthesis.\textsuperscript{38,56,63}

A critical difference, however, is with the transmitter(s)/receptors(s) involved, along with pathways for their stimulation. Thus, in contrast to acquisition, extinction probably engages GABA-containing inhibitory (inter)neurone populations in the amygdala.\textsuperscript{38} Evidence suggests that one source of activation of these inhibitory neuronal pools is efferent input from the medial prefrontal cortex.\textsuperscript{68} Possibly signalled by activity at opioid receptors in the brainstem peri-aqueductal grey matter.\textsuperscript{63,69} However, GABA (acting at GABAA receptors) may not be the only transmitter system responsible, directly or indirectly, for inhibition of output in the amygdala. Recent research into mechanisms for the acceleration of extinction learning and its (therapeutic) consequences, has identified the inhibitory transmitter glycine (acting at its site on the NMDA receptor). Therapeutic blockade of dopamine (D\textsubscript{3}) and adrenergic (\alpha\textsubscript{2a}) receptors has also proved beneficial.\textsuperscript{38} Marsicano et al.\textsuperscript{70} claim that endogenous cannabinoids and their receptors are critically involved in the extinction of aversely acquired (pain) memories. It appears that there are probably several means of creating and/or enhancing extinction, some of which operate through different (inhibitory) mechanisms. Together, the various mechanisms all have the ultimate objective of inhibiting activation of the amygdala by innocuous (neutral) stimuli.\textsuperscript{56} The therapeutically relevant outcome is achieved by turning this excitation into inhibition, thereby ‘masking’, or extinguishing, an associatively learned pain memory along with its undesirable clinical consequences (in this case, posture- and movement-evoked pain).

**Predictive learning**

The fact that effectively the same stimulus, in this case movement, can have both excitatory and inhibitory capabilities, albeit under different circumstances, clearly has its drawbacks (stimulus ‘ambiguity’). Nevertheless, it is an effective mechanism for temporary learning, and the subsequent suppression of potentially disruptive physiological, emotional and motoric responses to what are in reality safe, functionally necessary experiences or activities\textsuperscript{43} – namely, the routine execution of pain-free everyday movements. Therefore, in terms of the present proposal, it is when the associative memory system is being inappropriately reinforced and goes on attending and responding to ‘poorer rather than better predictors’ of (real) danger,\textsuperscript{40,43} that the
potential for disabling movement evoked CDNSLBP develops.

To comprehend the predictive aspect of associative learning and its implications for clinical MP better, it is useful to recall the learning theory premise recently reiterated by McNally and colleagues. In brief, this states that associative learning is the product of a discrepancy between actual and expected outcomes, so that learning occurs only for events, or sensory inputs, that the nervous system is not expecting.63,69

Put another way, (associative) learning with respect to both memory acquisition and its extinction is the result of an ‘error of prediction’.40

Explicitly, acquisition and extinction of associatively learned (pain) memory are due to failure on the part of the neutral stimulus to predict accurately the outcome of being, or having been, paired with pain. Acquisition, or excitatory learning, occurs when the actual outcome exceeds the expected outcome. That is, where the sensory consequences of the association are underestimated. This is the situation that arises when movement, a stimulus (afferent input) that is normally painless, is now painful. On the other hand, extinction, or inhibitory learning, occurs when the expected or predicted outcome exceeds the actual outcome, and the sensory consequences of the neutral stimulus have been overestimated. In this situation, the severe pain formerly provoked by (conditioned) movement subsequently fails to materialise. Either way, the accompanying sensory experiences are not what the nervous system is expecting. As a result, it is alerted to, learns from, and memorises them in an excitatory or inhibitory context (see McNally and Westbrook).40

**EXTINCTION WITH MP**

Extrapolating the above discussion to the present proposal, intrinsically innocuous sensory input produced with movement, propriopception, does not generally signal pain. When it is perceived as (acute) pain, this constitutes a variation from the norm of sufficient magnitude to attract the attention of the nervous system. The result is that both sensory inputs generated by movement, propriopception and (the ‘teaching’ input) nociception, now become associated in the signalling of pain. As the inflammatory process along with its profuse nociception subsides, propriopceptve input may continue to ‘predict’ pathological pain erroneously (see below). Furthermore, it goes on doing so until suitable ‘exposure without danger’ (e.g. MP) convinces the nervous system of its error. Graduated movement in the absence of nociceptive reinforcement then induces the innocuously produced input, propriopception, to initiate extinction of an aversely acquired associative memory. It is able to do so because the lack of nociception (‘pain’) is unexpected, and the nervous system is alerted to the change.40,69

It should be evident that, in this case, it is not simply the elimination of nociception that initiates extinction (and, therefore, recovery); the nervous system also needs to be aware that this has occurred. Lovibond71 goes further, maintaining that successful extinction probably requires both ‘low’ (automatic, unconscious) and higher (expectation, conscious) level nervous system function. If this is so, then a conscious contribution to extinction further emphasises the importance, and therapeutic value, of providing (CDNSLBP) patients with suitable ‘information’ (explanation and re-assurance).2,15 ‘Patient preparation’, therefore, has several relevant objectives. These include validation of patients’ pain experience, disabusement of maladaptive beliefs, and re-assurance regarding the ‘meaning’ of pain, the ‘safety’ of active movement and the potential for a positive prognosis.2,9,15,72 This is considered necessary for excessively fearful and overprotective patients about to undergo exposure to formerly threatening and avoided trunk movements.2,27,28

Evidence indicates that, in such circumstances, anticipated pain may be as feared and aversive (hence emotionally ‘reinforcing’) as the evoked pain itself.9,12,27,28

In this paradigm, inhibitory learning is the result of graduated (‘safe’) exposure to the feared stimulus. Without this experience, the nervous system is unable to learn that it is overestimating the outcome when it predicts that afferent input produced by (therapeutically modified) everyday movement is invariably (and severely) painful. This is one clinically relevant example of inhibitory learning through ‘violation of (sensory) expectation’.40 In this situation, it is hypothesised that the graduated physical exposure strategies employed by MP can effectively restore an original ‘uncontaminated’ pattern of propriopceptive afferent input. This normal innocuous input then has the ability to initiate extinction of an aversely acquired pain memory. (As discussed further on, another way in which an MP intervention can initiate extinction of CDNSLBP, is by creating a permanent change in the customary pattern of propriopceptive afferent input generated by everyday postures and movements. A change of this nature may be particularly relevant for some clinical presentations of CDNSLBP (see below).)
Clinical presentations

It is well known that CDNSLBP patients tend to be fearful of movement, especially where they anticipate that this will evoke pain. The potential exists for patients to continue to focus on pain and overprotect a pain site long after the effects of an original triggering event (peripheral nociceptor sensitisation) are considered to have subsided. It is hypothesised that, in this situation, reinforcement of an aurally acquired pain memory is by relatively normal proprioceptive afferent input which has been temporarily ‘contaminated’ by undue protection and avoidance, for example, ‘antalgic’ postures, ‘guarded movements’. Excessive attention (hypervigilance) to pain and the pain site has been said to help keep central pain pathways ‘sensitised’. Together, excessive ‘focusing’ and protective behaviour deprive the nervous system of the opportunity to learn about, and correct, its overestimation of the consequences of normal proprioceptive afferent input evoked by ‘unguarded’ everyday movements. Patients who demonstrate avoidance of movement and antalgic postures would, therefore, be expected to respond favourably to cognitive-emotional and physical ‘desensitisation’ protocols of the type provided by MP. (The interested reader is referred to O’Sullivan and Zusman for details regarding ‘patient preparation’ and ‘graduated exposure’ to mechanical stimuli, along with their proposed intrinsic sources of inhibition.)

Segmental instability due to muscular insufficiency is also said to be common with CDNSLBP patients. For patients with this diagnosis, pain and disability remain long after inflammatory consequences of a triggering episode have ended. Chronicity is claimed to be the result of loss of functional control around a so-called ‘neutral zone’. This is thought to render the inert osseoligamentous structures vulnerable to ‘injury’ through repeated minor trauma. Currently, evidence for certain claims, beliefs and extrapolations for this clinical diagnosis and its management with MP is felt to be insufficient. Importantly, such ‘impairment’ variations from the ‘normal’ would be expected to create unique patterns of proprioceptive (mechanoreceptive) afferent input. This input is likely to include ‘ends-of-range’ mixtures conveyed by both large and some smaller fibre joint and muscle afferents. In common with the rest of society, these individuals sustain periodic minor trauma and peripheral tissue insult leading to (self-limiting) bouts of back pain. It is proposed that these episodes result in arousal, and spontaneous or therapeutic resolution of a central ‘pain memory’ (extinction) that is, nonetheless, being progressively ‘strengthened’. At some point (a critical incident, sufficient number of ‘pairings’, psychosocial influences?), the pain, at least with respect to certain ingrained postures and movements, fails to resolve. Again, it is hypothesised that one reason for this common clinical history might be that their characteristic (‘mixed’) pattern of proprioceptive afferent input acquires the ability to go on exciting relevant supraspinal neurones after pathologically produced nociception has disappeared.

Initially, idiosyncratic patterns of proprioceptive afferent input and pathologically produced nociception became ‘strongly’ associated at central nervous system synapses as described earlier. The proprioceptive input now ‘learns’ to signal pain; later, when the acutely produced (inflammatory) events have subsided, it continues to do so by reinforcing a powerful pain memory. More or less unavoidable mechanical reinforcement of this memory (ADL) is likely to be augmented by cognitive emotional consequences of mounting distress in these often poorly understood and managed chronic pain patients. The clinically relevant effect of the two sources of memory reinforcement is to sustain the sensory and motor responses that make up continuous postural, and direction-specific movement-evoked (‘mechanical’) back pain.

It is posited that the ability to perform everyday dynamic and static movements without pain would necessitate a change in the pattern of peripheral afferent input they habitually produce. In learning theory terms, a ‘new’ pattern of movement-produced proprioceptive afferent input with no relationship to nociception, would then be able to establish an ‘opposing inhibitory association’ with the behavioural responses, and initiate extinction. An informed movement-based intervention such as MP appears to be a particularly (cost)effective way of achieving this ‘pattern change’ and, thereby, inhibitory outcome.

In this situation, a ‘new’ pattern of proprioceptive afferent input created by MP initiates extinction because it not only fails to signal pain; it also becomes the ‘teaching input’ for signalling ‘no pain’. Associative (predictive) learning theory decrees that the nervous system would attend to and learn from this ‘new’ movement-produced input because it differs from that which it is accustomed to receiving. Not only is the pattern of afferent input...
noticeably different from that customarily evoked by habitual postures and movements with these ‘mechanical’ CDNSLBP patients, it is also one that is not associated with nociception. The proposal then is that treatment strategies intrinsic to MP are able to eliminate a customary source of mechanical reinforcement, and establish a different ‘dissociated’ pattern of proprioceptive afferent input in its place. Together with a decline in cognitive-emotional drive wrought partly by ‘patient preparation’ and now direct experience, this ‘new’ pattern initiates extinction of an aversely acquired pain memory.

**Clinical relevance**

In order to qualify for serious consideration, any hypothesis concerning mechanisms needs to be compatible with (most of) the available evidence as well as the clinical experience. If the actual basis for movement-evoked CDNSLBP is somehow bound up with (the pattern of peripheral) afferent activity produced during ADL then, whatever their rationale, MP clinical strategies should be capable of targeting and altering this input.

As mentioned earlier, one way in which CDNSLBP patients deal with fear of, and aversion to, various types and directions of everyday movements and their actual or anticipated consequences, is by engaging in excessive protection of the painful site. These ‘guarded’ postures/movements are expected to create several sources of unusually intense, sustained patterns of proprioceptive afferent input. This (highly conscious) input becomes associated with, and, it is proposed, subsequently continues to reinforce, an aversely acquired chronic pain memory. The influence such psychosocial factors have on patients’ ‘guarded’ postures and styles of movement has clearly emerged from the clinical studies.

This influence is partially addressed with MP by providing patients with suitable information namely, explanation concerning causal mechanisms, reassurance, advice, direction, feedback. ‘Patient preparation’ along these lines is said to help break a vicious circle of ‘excessive attention and protection’, and assist in the resolution of this ‘yellow flag’ contribution to chronicity. Together with the early resumption of graduated physical activity (which it facilitates), the provision of appropriate information is a prominent ‘clinical best practice’ guideline recommendation for the management of back pain in general.

In addition to ‘patient preparation’, MP employs a number of physical strategies that have the potential to reduce mechanical reinforcement of an associatively learned pain memory. These include relaxation and breathing control techniques, directional pelvic tilting, active postural adjustments, structural ‘unloading’, selective flexibility exercises, proprioceptive awareness retraining, active support/core stabilisation (isolated muscle contraction), and inhibitory passive stimulation procedures. As discussed above, the proposed mechanism involves ‘safe’ graduated exposure to new patterns of peripheral afferent input. It is emphasised once more that ‘patient advice’ alone is not considered sufficient for these cases of CDNSLBP; personal experience of the (pain-free) sensory, and functional, consequences of individually prescribed and personally ‘mastered’ MP physical routines is deemed necessary for their recovery.

Regardless of current rationale, the physical procedures would be expected to result, sooner or later, in vital changes in the nature and composition of movement-evoked peripheral afferent input. This then leads to cessation of mechanical reinforcement of an aversely acquired pain memory, and its subsequent replacement with a new form of inhibitory learning, extinction. The CNS responds because it is alerted to the ‘new’ input, learns that it is not associated with nociception, experiences for itself that movement is now ‘safe’, and concludes that it has made an error of prediction. Hence, if, extinction of an associatively learned pain memory is a therapeutic mechanism of significance with MP, then clinically distinct presentations of CDNSLBP would benefit from different types of ‘change’ in pain-associated (patterns of) peripheral afferent input this intervention is proposed to create.

**Final comments**

In most respects, acute ‘non-specific’ back pain would seem to be no different from any other type of short-lived regional musculoskeletal pain. It is probably initiated by inflammatory chemicals (however present), with varying degrees and duration of peripheral and central sensitisation. Pain, along with its behavioural consequences, would be expected to subside steadily as these spontaneously resolve. Indeed, this appears to be the typical history of most episodes of back pain across the globe, for which no treatment is usually sought (or is available/affordable).

Nevertheless, recurrences and remissions are common, as are day-to-day fluctuations in symptom intensity. Although still unclear, certain natural or acquired biomechanical characteristics may render...
some individuals more susceptible to recurrence (‘relapse’) than others. Whether this ‘phenotype’ also renders the holder permanently vulnerable to ‘injury’, and so descent into CDNSLBP, is another matter. There is currently no evidence for on-going clinically relevant peripheral (nociceptor) sensitisation with CDNSLBP patients, as has been suggested.\(^2\)

Issues such as these are important for several reasons. One is when it comes to the use of ‘information’ as a means of assisting patients to allocate attention to and actively comply with (often rather difficult) MP routines.\(^7\) Rational explanation and re-assurance are among acknowledged verbal strategies for encouraging patients to venture ultimately into feared and patently painful (directions of) active movement. While clinicians know that such ‘exposure-desensitisation’ is vital to their rehabilitation, patients need to be given an acceptable reason(s) to engage in activities that are frequently against their better judgement and personal experience. What significant difference would it make to the patient whether on-going peripheral nociceptor sensitisation were chronic (as has been claimed) or acute? Both are likely to be perceived as pathologically valid reasons for avoiding (specific) activity. How would hearing this explanation re-assure patients that movement-evoked chronic pain was now ‘different’ from their original pain, and not ‘dangerous’? Similarly, surely at least some patients told that their chronic movement-exacerbated pain and disability was the result of an acquired ‘instability impairment’ would begin to wonder why they alone were so afflicted. If pain-mediated muscular insufficiency, with ‘injury’ vulnerability, is such a common consequence of just a single episode of self-limiting back pain, why aren’t there infinitely more individuals crippled with CDNSLBP?

The ‘pain memory’ hypothesis provides an alternative (additional?) basis for the periodic recurrence of back pain, along with eventual onset of CDNSLBP in susceptible individuals. Namely, the potential for an extinguished associatively learned pain memory and its behavioural responses to sporadically re-appear or ‘relapse’. Relapsed memories, in turn, may (or may not) also subsequently recede, either spontaneously or with professional help. Together, this explanation complies with common clinical observations for ‘non-specific’ back pain, and relates to variously interpreted response to physical treatment. With regards to treatment, insight into recognised mechanisms for pain memory relapse does suggest several physical intervention enhancement strategies for reducing the likelihood of ‘recurrence’ of (non-specific) back pain. Among those suitable for extrapolation to treatment with MP would be ‘overtraining’, on site training, retrieval ‘cueing’ and ‘booster’ extinctions (see Bouton\(^66\)).

Thus, experimentally, two of the four recognised mechanisms for relapse of an extinguished associative pain memory (hence, back pain), ‘re-acquisition’ and ‘reinstatement’, involve a repeat bout of nociceptive input.\(^66\) This would be in keeping with the common clinical experience of patients’ reports of further tissue insult (‘strain’). Physiologically, the arrival of nociceptive input at supraspinal synapses, re-establishes the capacity for a formerly conditioned neutral stimulus (movement) to resume evoking clinically relevant pain-related responses (symptoms and signs). For reasons discussed, instead of resolving naturally or with the help of routine professional intervention, sufficient (in some cases just the one?) ‘memory relapses’ of this nature with susceptible individuals may end in CDNSLBP (see also Flor\(^85\)).

With the two remaining mechanisms, relapse is seemingly spontaneous. This is also a commonly observed clinical characteristic of ‘non-specific’ back pain, although rarely reported when litigation or compensation is involved. For the mechanism known as ‘spontaneous recovery’, re-appearance of

![Figure 1 Summary scheme.](image-url)
(movement-evoked) pain is simply a function of time. The cause of, and variables that influence, ‘spontaneous recovery’ are not fully understood, and appear complicated. Whatever the explanation, despite initial reports to the contrary, careful questioning of patients exhibiting recurrent ‘non-specific’ back pain may uncover a history of this type.

Finally, and no less significant from a clinical perspective, there is the mechanism known as ‘renewal’. In this case, following extinction in one setting or ‘context’ (e.g. clinic), all that is required for the resumption of inappropriate behavioural responses (symptoms and signs) to a normally innocuous or neutral stimulus (e.g. movement) is suitable exposure to the former pain-associated (‘dangerous’, threatening) environment. Bouton considered ‘renewal’ to be the most potent and pervasive of the relapse mechanisms, and regards spontaneous recovery (and somewhat differently, reinstatement) as simply a change in temporal context. Sensitivity to environment or ‘context’, physical and temporal, does raise the issue of return to some task-related setting following recovery (work), especially were this an ‘unhappy’ one, and patients’ subsequent reports of recurrent episodes or pain perceived to linger months, or even years, later.

To conclude, neither purely biomechanical nor psychological ‘susceptibility’ to episodic or chronic non-specific back pain fully account for still mystifying structural and functional inconsistencies seen both between and within symptomatic and asymptomatic individuals. Mechanisms of an associatively learned memory for pain along with its potential for extinction with physical exposure-desensitisation protocols, is another perhaps more ‘encompassing’ explanation. It may be possible to explain at least some cases of chronic non-specific low back pain, and its response to treatment with MP, in these (neurological) terms.

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