Frontiers in Chronic Pain: A Rationale for a New Understanding of Non-malignant Chronic Pain without Sufficient Explanatory Pathology and Subsequently a New Paradigm for Improved Treatment

Author: Christine Sutherland
Author contact:Email: office@lifeworks-group.com.au

Highlights

- We re-affirm that there is no current treatment for non-malignant chronic pain without sufficient explanatory pathology which provides any clinically significant relief for the majority of sufferers.
- We examine verified and robust evidence for a new theory of the mechanisms behind chronic pain which points to an entirely new direction of treatment.
- We propose a novel treatment for non-malignant chronic pain without sufficient explanatory pathology which fully addresses the identified mechanisms and which has previously been successfully trialled in small studies.

ABSTRACT

In a previous paper we noted that to date there is not any treatment for non-malignant chronic pain without sufficient explanatory pathology that provides any significant relief of pain for the majority of people, and that this includes the newer multi-disciplinary or "comprehensive" chronic pain programs. It is after all well accepted but deeply unfortunate that current treatment programs stress that the goal is not to reduce pain, but about helping the patient to achieve a higher quality of life despite the pain.

This paper explores updated research in order to delve more deeply into robustly demonstrated mechanisms of non-malignant chronic pain without sufficient explanatory pathology, being both conditioned (where pain signalling is a response to a conditioned stimulus or set of conditioned stimuli) and due to general sensitisation as a result of a hyper-alert nervous system, which itself is a consequence of comorbidity and/or lifestyle issues such as sleep disturbance, activity levels, nutrition, and general stress, all which can be regarded as "allostatic load".

In addition we examine recent research relating to a novel extinction strategy which addresses the conditioned aspects of chronic pain, and which may also be useful as an adjunct to treatment of comorbidity and lifestyle issues, in order to enable greater magnitudes of resolution of pain, for far more people than is currently the case.

Finally we make a plea for funding and collaborators to subject this novel treatment strategy to much wider testing.

INTRODUCTION

When an intervention or strategy does not work, or has poor predictability in terms of expected outcomes, we must suspect that the strategy, in terms of its target, is flawed. Likewise, a flawed strategy generally arises from flawed theory.

This is the situation we have found ourselves in at this time, with no intervention, or combination of interventions, providing predictability in the treatment of chronic pain, and no intervention or combination able to provide relief for the majority of sufferers[1].

We must therefore consider that the strategies being applied in the treatment of chronic pain are flawed, and that current theories of chronic pain may be likewise flawed. This paper is an attempt to largely rewrite the theory, based on aggregated, robust evidence from a varied array of researchers, and firmly point to a novel direction of treatment based on that updated theory.

In this paper the term "chronic pain" specifically refers to non-malignant chronic pain without sufficient explanatory pathology, and this includes almost all non-malignant chronic pain, being back and neck pain (the vast majority of chronic pain presentations) as well as post-injury and post-surgery pain, phantom pain, and fibromyalgia. It does not include pain which is labelled chronic but which is acute in nature, such as endometriosis, adenomyosis, and rheumatoid diseases, because acute and chronic forms of pain are entirely different in nature, as will be shown below.

When we use the term "chronic pain" here, we specifically mean pain which does not have sufficient explanatory pathology. The reason that we include back pain in this group is that spine issues do not usually correlate with back pain (this is why MRI and other imaging diagnostics are no longer generally recommended for back pain – one is not likely to see anything different about the spine of someone with back pain than of someone with the same damage but no pain). So although there is identifiable pathology, it does not explain the pain.

With a global economic burden likely to be considerably in excess of a trillion dollars per year (over $600 billion in the USA alone) and a health burden that affects at least 20% of human beings, their families, communities, and workplaces, we have a tragedy of massive proportions which is not currently being significantly helped by anything.

So the question we are forced to consider is, why do all of the current treatments for chronic pain, being pharmacological, physical/device/surgical, and psychological, have so little impact on people's pain? Why are these treatments failing so spectacularly?

We will show that current treatments do not address the cause of the chronic pain, and in fact mostly do not even recognise the cause of chronic pain. Even where extinction is attempted, the methods used are invariably inhibition strategies (eg CBT, mindfulness, desensitisation), which are notoriously ineffective in humans. By setting out a rationale for a new understanding of

chronic pain, in particular the mechanisms involved which are clearly related to associative and non-associative conditioning, and by detailing a new methodology for achieving rapid extinction, we hope to show the way to new and better treatments which can finally resolve chronic pain for the majority of people.

Background

Chronic pain is widely considered to be a "brain problem" rather than being attributable to any pathology which wholly or partly explains the pain.

The brains of chronic pain sufferers differ from brains of healthy individuals. Some researchers refer to this as "altered chemistry" or even as "changes in the brain", but there is a growing body of evidence that these changes are not really in the brain structure, but in brain activity, and when that activity returns to homeostasis, structure (eg regrowth of the hippocampus) also returns to normal.

In more recent times chronic pain has been regarded specifically as a "memory" problem and attempts have been made to "recall and erase" the pain memory. Both de Koninck[2] and Basbaum[3] have detailed the brain activity involved in chronic pain and shown that it is certainly learned. De Koninck's work in particular has focussed on reducing chronic pain by preventing reconsolidation of learned pain signalling.

We note two overlapping changes to brain activity that are apparent in chronic pain presentations, as demonstrated by fMRI:

A) Central or general sensitisation

When the nervous system becomes overly sensitive, nociceptive stimuli are perceived in an amplified way. Studies comparing pain perception to novel pain stimuli (eg electrical stimulation, extreme cold) show that chronic pain patients report higher levels of pain than do healthy subjects. Latremoliere and Woolf[4] showed that this central sensitisation can be entirely independent of peripheral input.

B) Learned (conditioned) pain signalling in response to specific stimuli

In this case the person experiences pain totally or partly in the absence of nociceptive stimuli, in direct response to thoughts, feelings, actions, or other stimuli. This is conditioned pain, where the brain virtually creates pain signals through learned sensitisation or learned disinhibition mediated by associative and non-associative processes, primarily via the amygdala, but involving the basal ganglia, cerebellum, thalamus and other structures that control memory and learning.

In recognition of biochemical processes driving brain activity for what is essentially two different but overlapping mechanisms (general sensitisation, and conditioned learning both associative and non-associative) pharmacological treatments have attempted to modulate the neurochemistry involved, but have failed spectacularly to provide relief for the majority of people.

After all, we do not at this time have drugs which selectively erase memory or selectively extinguish conditioned responses or selectively erase a memory, and neither do we have drugs which effectively and selectively inhibit sensory stimuli. So it is understandable that the proportion of people who are getting some kind of relief from pharmacological strategies is indeed in the minority, and also explains why that level of relief is so close to placebo. These patients may be getting real relief, or may be experiencing regression to the mean, or false attribution, or other well-known confounding issues.

Similarly, special exercise programs do not reduce chronic pain. We do know that improved sleep, good nutrition, and appropriate levels of activity are associated with reduced pain levels, but these things are the very basis of health and wellbeing and are essential to optimise health for everyone, including chronic pain patients.

Surgery and devices have likewise been exposed as problematic rather than helpful, in the majority of cases either not working or even making the pain worse.

Finally, psychological approaches such as CBT, mindfulness, and "pain education" have shown themselves to be universally ineffective in reducing chronic pain. There is some very minor evidence for short-term improvement in quality of life scores, but not for pain reduction, and not even for significantly increased functioning. The improvement in quality of life scores could be due solely to having human attention and empathetic support, as even these modest outcomes only appear when compared with waiting lists. In other words these various psychological interventions are only superior (and only very modestly superior) when compared with doing nothing.

So to date the best we've been able to do for chronic pain patients is to support efforts to improve lifestyle, including trying to resolve the comorbidity that so often accompanies pain, such as depression and anxiety, and sleep dysfunction.

It is our view that chronic pain can be resolved, and that this requires a deeper appreciation of the demonstrated mechanisms of chronic pain, together with a dual approach to treatment:

A) Allow the nervous system to return to homeostasis so that non-noxious stimuli are no longer incorrectly perceived as painful. This will involve quality of life issues as well as comorbidity.

B) Identify and extinguish the conditioned learning that effectively produces pain signals in the absence of sufficient explanatory pathology. Comorbidity may also have become conditioned, and may in turn serve as a conditioned stimulus to pain signalling.

Since these factors (sensitisation and conditioned learning) overlap, it is probably not possible to eliminate chronic pain without attending to both, in most cases.

Difference between acute pain and chronic pain

Acute pain is an adaptive neurological process which benefits us by forcing us to move quickly away from the source of pain in order to avoid further damage, and drives us to take action to protect/heal and to support the healing process.

Acute pain is not entirely nociceptive, as the context in which the painful event occurs has a direct impact on the level of pain experienced, or indeed whether pain is even felt at the time of

insult. It is not uncommon for people in the heat of battle or some other trauma to have no memory of being hurt, but realising later that they have sustained a significant (even life threatening) injury.

However in every case the experience of acute pain is directly explained by nociceptive mechanisms.

In contrast to this, chronic pain (of the type we are describing here, which is the vast majority of presentations) is not explained by nociceptive mechanisms and may even be wildly different in nature or in location to the "old" injury which the chronic pain has developed from.

This non-nociceptive nature is possibly most obvious in the case of most back pain, which is in turn the most common of chronic pain presentations. People with back pain may or may not have degenerated or bulged discs, deterioration of the vertebrae, or other spine problems. The prevalence of these issues is not different in people who do not have back pain, even when we look at populations of elite athletes[5]. So the damage does not explain the pain. It appears this type of nociceptive stimuli becomes habituated for most people, but not for the 20% of chronic pain patients.

How Chronic Pain Arises

Chronic pain invariably begins with some kind of acute episode or trauma. Some 80% of people who suffer an injury or trauma go on to heal as well as possible, with little or no pain after an expected recovery phase.

However at least 20% of people do not achieve this pain free state and the pain can remain, become worse, spread to other areas, involve other non-pain symptoms, and can be accompanied by comorbidity and other problems.

Many researchers have investigated and described measurable biochemical changes in neurological function, but have not necessarily considered whether learning/memory processes could be causative of those changes[6], even when noting the precise similarity between neurological processing in anxiety/fear, and chronic pain.

In recent years there has been increasing interest in the transition from acute to chronic pain conditions and a growing acceptance of a new paradigm for chronic pain that does not in any way detract from earlier studies, but rather encompasses and explains them.

In terms of brain activity we can now see that conditioned pain can usefully be regarded as being similar to or identical to conditioned fear or conditioned anxiety[6], for example. The mechanisms are the same.

The many excellent fMRI studies which have been carried out over the years have provided the strongest possible evidence that chronic pain is associated with conditioned brain activity, mediated primarily via the amygdala region. It is by now unquestionably clear that chronic pain in many cases is not nociceptive in nature, but rather is an allostatic state established through "plastic and (mal)adaptive processes in the central nervous system[7–9].

Other researchers have more specifically pointed to associative and non-associative conditioning as an avenue for such "noci-plastic" changes in brain activity.

Neugebauer[10] investigated mediation of chronic pain via the amygdala region and demonstrated changes in activity in that region associated with the development of chronic pain, and also demonstrated via fMRI that acute pain and chronic pain utilise different nerve paths.

Lewis et al[11] carried out a systematic review and meta-analysis investigating chronic pain as conditioned activity in the brain, with a focus on lower back pain, the most common of all reported chronic pain presentations.

De Koninck et al[2] presented a scientific exposition of his "recall and erase" theory where he describes chronic pain as a "error of memory" which may be simultaneously triggered and extinguished, and demonstrated that reversal of hyperalgesia was possible. However we propose a three-fold point of difference with De Koninck's perspective: firstly De Koninck, like several others, is focussed on pharmacological disruption in order to create extinction of the "pain memory". This is unnecessary, as sensory disruption is faster, easier, safer and more precise and is therefore more highly efficacious[12,13]. Secondly De Koninck under-estimates the complexity of conditioned responses which may be at play. Sets of conditioned responses associated with non-pathological pain signalling are frequently highly complex and can encompass literally every aspect of a client's life. Thirdly De Koninck does not address the other factor in production of chronic pain signalling, being the comorbidities and lifestyle issues that create or maintain a hyper-reactive (over-sensitive) nervous system.

Relative to this hyper-reactivity, in an experiment on the adult fruit fly (Drosophila), Khuong et al[14] first damaged a single nerve in one leg of the insect, allowed it to heal, and then tested sensitivity in all limbs. They found that despite full healing, the insect was now much more sensitive to stimuli and exhibited pain avoidance behaviour for normal stimuli. The team found that signals in the ventral nerve cord (equivalent to the spinal cord in humans) were behaving differently and failing to damp down normal sensations due to disruption of GABA (the chief inhibitory neurotransmitter Gamma-Aminobutyric acid) signalling. This could explain why there is such a very small proportion of responders to the gabanoids.

Still other researchers also regard most chronic pain as non-nociceptive and describe an evolution from acute pain to pain which is self perpetuating[15,16–18], partly via a nervous system which has become hyper alert, and partly via learned pain signalling via the amygdala[19].

Supporting De Koninck's hypothesis is a study by Berry at al[20] showing that an insufficiency of the neurotransmitter dopamine causes a failure of conditioned learning in Drosophila. Since dopamine deficiency can play an important role in depression, as shown by Dunlop et al[21] this may support the noted correlation between depression and chronic pain. This study may also have uncovered some of the chemistry of disruption of reconsolidation, at least partially answering the question "how does extinction caused by disruption of reconsolidation actually occur?"

Migues et al[22] made a similar discovery in rats. The team found that when they blocked removal of AMPA receptors (these are ionotropic transmembrane receptors for glutamate, which is a key element involved in memory and learning) rats were prevented from "forgetting" conditioned learning. As Hardt[22] commented "Forgetting is not a failure of memory, but a function of it". Most people (around 80%) "forget" their pain responses after healing. Around 20% do not, and the natural culling or otherwise of AMPA receptors could

also be a key for some people. Perhaps countering this proposition is the ready example of "fibro fog" commonly experienced by fibromyalgia sufferers: they are already frequently "forgetting" but do not seem to forget how to produce pain signalling.

We note all of these hypotheses in relation to learning and extinction of learning are non-exclusionary for the theory of disruption of reconsolidation, and we pose the view that in terms of extinction they are all in fact describing a mechanism that supports disruption of reconsolidation as the key factor in extinguishing learning related to non-nociceptive pain signalling, and are each examining different parts or aspects of the overarching mechanisms of conditioning and extinction.

Many people working in the field of chronic pain now agree that chronic pain can be non-nociceptive in nature[23,24], and that it can be conditioned[13]. In particular Lorimer Moseley[16] has written extensively on non-pathological associations with pain perception, and Sabine Mlekush[25] has carried out trials demonstrating conditioned pain modulation.

Although we are far from the first to propose that chronic pain is entirely different to acute pain, we may be the first to propose that the majority of chronic pain is triggered by conditioned neurological processing, which may be readily extinguished through disruption of reconsolidation of the chronic pain "response".

However our theory of conditioned pain signalling has its detractors, as it has been challenging to replicate this conditioned learning of chronic pain in experimental studies of humans. In contrast it has been comparatively easy to induce anxiety or fear by use of a conditioned stimulus. Curiously, this failure to induce a conditioned pain response in humans (conditioned pain is well recognised in animals such as rats[26]) has led some researchers to believe that chronic pain is probably not conditioned in humans at all.

We counter that argument by not only pointing to the above animal studies that clearly demonstrate that chronic pain can become conditioned and that it can also be extinguished, but with the well-recognised view that in humans this learning of a pain response does not occur in isolation of other factors – there are significant risk factors involved in the development of chronic pain. A number of reviews have delineated various biosocial, genetic, epigenetic and environmental factors which may increase vulnerability to development of chronic pain[27–30]. The complex etiology of chronic pain is clearly difficult and perhaps impossible to replicate experimentally in humans.

This situation is even further complicated by the fact that most experiments which attempt to induce conditioned chronic pain in humans have been universally and necessarily done with healthy subjects – ie with people unlikely to develop chronic pain in the first place.

Finally, while responses such as anxiety and fear may be highly adaptive, chronic pain is maladaptive, and we know that adaptive responses are easier to achieve, less easy to habituate, and more likely to undergo recovery in direct contrast with non-adaptive responses which are more difficult to achieve, relatively easy to habituate, and less likely to undergo recovery post extinction.

Thus is it unsurprising that we do not have robust evidence of experimental induction of chronic pain in humans, and unsurprising that such a minority of people are even capable of developing chronic pain given "ideal" conditions and/or risk factors.

Methods of extinction of conditioned responses

History and theoretical foundation of SDR therapy

In the late 1990s/early 2000s, Sutherland ran four pilot studies utilising precursors to SDR Therapy for a wide range of amygdala-mediated disorders: chronic pain (two studies), clinical depression in the moderate-to-severe range, and academic and behavioural performance of children deemed "at risk". Three of these were written up, but one of the chronic pain studies had an efficacy of 100% and was discounted as an outlier and not written up. The paper on clinical depression was submitted for peer review and published in the journal Frontier Perspectives[12].

All papers demonstrated extremely high efficacy rates for SDR Therapy intervention, in the range of 85-90% (see "limitations" at the end of this paper), although at the time, without an overarching or well-developed hypothesis to more accurately describe the mechanism, SDR was referred to inadequately as "NeuroStim".

From 2001 to 2003 the author developed a theory of chronic pain being in most cases comprised of conditioned neurological activity rather than being nociceptive in nature. Until quite recently this theory had been broadly rejected by the medical community and is still widely regarded as novel. Today it is frequently misunderstood as "distraction", "desensitisation", "inhibition", "habituation" or even as "exposure therapy", all of which are inadequate explanations of the neurological processes involved and the outcomes obtained.

Prior to the above pilot studies Sutherland had for some time been experimentally eliminating chronic pain in clinic clients by exposing them to highly specific conditioned stimuli associated with the pain experience, including very precise and specific idiosyncratic thoughts or perceptions suspected of being associated with (or conditioned to) the pain (language, metaphor, meaning, beliefs, etc), while simultaneously introducing disruptive sensory stimulation, both literal and imaginal.

Sutherland proposed that chronic pain was largely due to conditioned activity in the brain and nervous system generally, and that this conditioned activity could be extinguished by disrupting the reconsolidation phase of the conditioned response, as described by Soeter et al[31], and also by Phelps and Hofmann[32], whose work will be discussed shortly.

Although excellent results with chronic pain (and other) clients seemed to be achieved, it was appropriate and necessary to put the work to the test in formal trials. After all, it is not unusual for therapists to mis-interpret temporary results in the clinic as robust outcomes which endure. Tracey et al[33] found that therapists tend to over-estimate their expertise, and also over-estimate effect size (if any) of the treatments they provide.

Due to lack of funding and other resources, those few clinical trials were very small (under powered, ranging from 8 to 25 participants) and not randomised, controlled, or double-blind, but consisted of treatment groups where patients were taught to self-treat. Approximately 50-60% of the groups eliminated pain entirely almost immediately, and a further 25-50% were able to reduce their pain significantly (ie, reduce their pain level more than 50%). At 2-year

follow-up only half of the treatment group were contactable, but in each of those cases the results had been maintained.

Since that time, thanks to the work of many other researchers, some working to investigate the mechanisms of chronic pain, and some working to investigate disruptive (rather than inhibitory) extinction methodology for conditioned responses, Sutherland has been able to develop that theory in a way that is deeply supported by the independent research of many others.

In particular we have seen the most exciting advances in extinction of conditioned responses from scientists studying memory and emotion, in particular Soeter et al[31] and Phelps and Hofmann[32]. These researchers have independently identified what they call the "reconsolidation phase" of a conditioned response, and they have shown that where the reconsolidation phase is "disrupted", there is a failure of the response that is permanent, ie; extinction is achieved quite rapidly and permanently.

Brunet et al[34] also demonstrated that a pharmaceutical agent, in this case the beta blocker propranolol (which blocks physical symptoms of anxiety), given before recall of a traumatic memory, significantly diminished PTSD symptoms over a 6-week period of treatment sessions, with results maintained at 6 month follow up. Brunet currently runs a clinic providing what he calls "reconsolidation therapy".

We note that although interesting and significant, the outcomes of Soeter's and Phelps and Hofmann's, and Brunet's trials of disruption of reconsolidation are not what we would regard as exciting. There are, in our view, major flaws in the methodology of these studies due to a lack of understanding of the nature of extinction of conditioned responses via disruption of reconsolidation, as follows.

Firstly when we talk about disruption of reconsolidation, this only has meaning if we are targeting a specific conditioned response. These authors failed to elicit a specific conditioned response and instead instructed participants to merely "think about", or focus on, a past or current event. None were teasing out the myriad of conditioned stimuli that produced the array of symptomatology they sought to resolve. This is too vague to specifically and accurately trigger a single conditioned response and would be expected to result in a statistically significant but less-than-exciting outcome.

Secondly Soeter et al and Phelps and Hofmann utilised pharmaceutical disruption, injecting substances into the amygdala region of the brain, or having participants ingest a pharmaceutical preparation (eg before or immediately *after* recalling a memory). This is also a critical error because the *timing* of disruption is critical – we must have precision – and it is doubtful that *simultaneous*, accurate triggering and disruption of the reconsolidation phase of the conditioned response could take place with such an imprecise protocol. The disruptive factor must occur simultaneously with presentation of a precise conditioned stimulus in order to create disruption during the reconsolidation phase and thereby achieve full extinction of the conditioned response.

Given these major flaws, the fact that outcomes were statistically and clinically significant in spite of them is indeed grounds for a high level of confidence. The proposed larger study of SDR Therapy to follow this paper intends to show what outcomes can be achieved when disruption of reconsolidation is executed with precision.

In contrast to our and others' hypotheses, it should be noted that the theory of disruption of reconsolidation does not have consensus even amongst those who study extinction mechanisms, primarily because they see the issue of extinction as being about a chemical process and are focussed on pharmaceutical solutions. Holding a hammer, they see the problem as a nail.

Inda et al[35] noted: "…. extinction was also dependent on protein synthesis, following the same temporal course as that followed during acquisition and consolidation. This last fact reinforces the idea that extinction is an active learning process rather than a passive event of forgetting". We argue against this interpretation by noting that by blocking protein synthesis for a period of time over which a conditioned stimulus was applied, the extinction of the conditioned stimulus was achieved, so one could equally say that the interference with (disruption of) *attempted* reconsolidation caused extinction.

Auchter et al[36] noted: "Fear extinction typically results in the formation of a new inhibitory memory that suppresses the original conditioned response" proposing that it was not so much an extinction of an existing conditioned response, as a learning of a new response which in some way "overwrote" or suppressed the old response. However the "extinction training" which they utilised in this study would certainly disrupt the reconsolidation phase of the conditioned response and Auchter does not provide evidence of a new memory. In fact they themselves cite earlier studies by Misanin et al[37] (who showed that an electric shock could disrupt reconsolidation and cause extinction), Nader et al[38] (who showed that blocking of protein synthesis during retrieval caused extinction), and Nader and Einarsson[39] who address "reconsolidation, where consolidated memories return to a transient unstable state following their retrieval, from which they must again stabilize in order to persist".

The theory that "new learning" inhibits an old conditioned response is popular but not demonstrated to date. In the light of the mass of neurological studies around conditioning and extinction it is more logical to consider that the old conditioned response simply fails or no longer exists because reconsolidation was disrupted.

Although the theory of "disruption of reconsolidation" is regarded as novel, Pavlov had already inadvertently discovered it over 100 years ago. In his experiments on salivation rates in dogs, he had set up conditioned responses to electric shocks. In his notes he wrote of his investigation into how far he could stray from the shock site (site of conditioned stimulus) before there was a failure of the response. He found that once he got to the point of failure of response, not only did the response fail at that point, but it was effectively extinguished permanently.

Pavlov had inadvertently discovered that if he sufficiently "messed up" (disrupted) the conditioned stimulus, he could achieve instant and permanent extinction. Unfortunately, rather than realising the enormity of his discovery, he wrote it up simply as a failure of the response, thus delaying an important advance for over 100 years.

Another well-accepted theory is the Rescorla-Wagner model[40,41] of conditioning. Part of this model states that there is a specific quantity of conditioned activity that can simultaneously apply to a single conditioned stimulus. If the stimulus is "overloaded" it may collapse, and the response be extinguished. This also fits with the theory of disruption of reconsolidation of conditioned responses.

Crossely et al[42] refers to "cognitive loading" as a method to "unlearn" conditioned neurological processes, but similarly to Soeter et al[31] and other researchers has not extrapolated from this in order to disrupt very specific stimulus-response pairs. Sutherland claims that weak, imprecise, or limited disruption of general sets of conditioned responses at play cannot provide optimal outcomes.

Similarly Bouton[43,44] proposed that when a conditioned stimulus is repeatedly paired with stimuli unconnected with the conditioned response, extinction could be achieved. In fact this is a further clear example of disruption of reconsolidation being a highly effective extinction strategy.

On the basis of in-clinic observation, her own previous trials, and in the light of well-accepted findings of other researchers, Sutherland makes four claims around a theory of non-malignant chronic pain without explanatory pathology, including a mechanism for the elimination of pain:

1. Non-malignant chronic pain without sufficient explanatory pathology (not acute pain) is almost always non-nociceptive and instead is generated by conditioned activity in the brain/nervous system

2. To permanently extinguish that conditioned activity, we need to identify precise conditioned stimuli, and disrupt the reconsolidation phase of each specific, active stimulus-response pair by *simultaneously* and accurately presenting the stimulus for the unwanted response with other equally (or more) intense stimuli

3. By extending the reconsolidation phase (in order to enable access to it) and simultaneously disrupting that reconsolidation via sensory stimulation, whether external/mechanical or internal/imaginal, we achieve extinction of the pain response

4. The hyper-sensitivity of the nervous system should be similarly treated, with attention also given to resolution of issues which create or maintain an aroused state, whether negative (such as stress) or positive (such as excitement) so that the system can be given time to return to homeostasis. This includes attending to issues of comorbidity, as well as critical lifestyle issues such as sleep dysfunction, environmental stress, nutrition/hydration, activity levels, etc

SDR (Sensory Disruption of Reconsolidation of conditioned responses) Therapy is the name given to specific techniques which have in common an action of rapidly and permanently extinguishing conditioned brain/nervous system activity by accurately disrupting the reconsolidation phase of a conditioned response. Since non-malignant chronic pain without adequate explanatory pathology is almost always entirely driven by conditioned brain activity, when we extinguish or "switch off" this activity, the pain ceases along with the activity. Sutherland claims that it can be a highly effective, very rapid and permanent way to eliminate or dramatically reduce chronic pain levels for most people.

To clarify and emphasise, the claim is that true chronic pain (ie; pain which is without sufficient explanatory pathology) almost always consists of conditioned responses of the brain and central nervous system, and that these conditioned responses can be extinguished very rapidly and permanently using sensory disruption strategies, rather than pharmacological strategies which are so imprecise and which carry a burden of serious side effects, and instead of physiotherapy programs and psychological techniques which are currently not working.

Conflict of interest: The author has spent the last 27 years investigating and refining SDR Therapy and currently teaches and supports psychologists wishing to implement SDR Therapy into their practices, specifically for non-malignant chronic pain without clear explanatory pathology, and generally for amygdala-mediated disorders and issues of all kinds, including depression, anxiety, phobias, addiction, trauma/PTSD, OCD, and many others.

Keywords: persistent pain, non-malignant chronic pain, chronic pain, nociception, amygdala, fMRI, mechanism of action, extinction, SDR Therapy, classical conditioning, associative and non-associative learning, disruption of reconsolidation

Recommendations for Further Research

The next research project should be a much larger examination of the impact of SDR Therapy on non-malignant chronic pain without sufficient explanatory pathology. At time of writing this study is ready to proceed as an online trial, due to COVID-19, and is accepting applications for suitable participants.

It should be recognised that this trial, being online only and despite attempting to provide quality personal support, cannot fully replicate a live therapy experience and a significant drop out rate is expected, along with significant but not outstanding outcomes.

Following this, more extensive, randomised, controlled trials of the complete SDR program should be conducted in order to assess the final outcomes of treatment over the 16 sessions that are recommended in a staged process over 8 months. Thoroughness is essential as we know that when extinction is incomplete, there is always likelihood that recovery of the unwanted conditioned response/s can occur. Rosas et al[45] provide an excellent rationale for recovery post extinction.

However these trials should seek to avoid confounding elements which have so far plagued studies on a range of other treatment strategies and this should include testing against appropriate controls, which given the current interest in multi-disciplinary programs, should be comprehensive chronic pain treatment strategies in hospitals and pain clinics, which at least have higher efficacy rates than "treatment as usual" as seen very clearly in the Deloitte report[46] and others[47].

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