INTRODUCTION

More than 100 years after its modern revival, identifying mechanisms underlying the clinical efficacy of musculoskeletal (formerly ‘manipulative’) physiotherapy (MP) is still surprisingly elusive. This is particularly regrettable given that the same period witnessed enormous, unprecedented advances in all areas of orthodox medical science.

Reluctance to hypothesise as to the histological and (patho)physiological mechanisms of such a fundamental factor as joint hypomobility and its ‘change’ with (passive) movement does not help elevate the status of MP. Paying little more than lip service to the broader basic sciences while effectively clinging to a ‘cookbook recipe’ approach to health care retains physiotherapists at the level of technicians or ‘craftspersons’. Parties with an interest in maintaining the profession at this level are thus provided with an argument for doing so. Moreover, to orthodox mechanisms-trained medical professionals in particular, such an approach to health care is anathema.
order to enlist and hold the support of these and other ‘stakeholders’, physiotherapists have a professional obligation to research and reveal the basic nature of ‘conceptually’ indispensable entities (e.g. joint ‘stiffness’). 7–9

Given the relative dearth of scientific evidence concerning ‘structural’ mechanisms, it is not surprising that attention within the profession turned to neurologically based investigations of MP. In particular, these addressed the role that had long been proposed for ‘manipulation’. Namely, mechanisms of passive movements as a form of stimulation therapy for the (temporary) relief of pain. 9,10 One consequence of this research was to stimulate an upsurge of interest in biological mechanisms for the cause and treatment of the symptom pain. Pain mechanisms and management have been the focus of intense international multidisciplinary investigation over particularly the last quarter of the 20th century and beyond. 11,12 Nowadays, in-depth exposure to this information is a routine component of the more worthwhile physiotherapy courses world-wide.

The following discusses neurological mechanisms for clinically observed consequences of MP passive and active movement-oriented interventions. The long hypothesised mechanism, (mechanical) stimulus mediated arousal of the bodies ‘in-built’ pain inhibitory system, is now supported by several lines of evidence. Two further mechanisms, forms of learning known as ‘habituation’ and ‘extinction’, are proposed. These would have more enduring effects but currently lack specific evidence.

PASSIVE MOVEMENTS AS STIMULATION THERAPY

The results of a recent study by Skyba et al. 13 provide further endorsement for the proposal that peripheral afferent input produced by joint mobilisation (‘grade III’) activates supraspinal descending pain inhibitory systems. A growing body of anatomical, physiological and behavioural evidence from experimental, basic sciences and clinical studies strongly suggests that such a neurological mechanism would contribute to the clinical efficacy of MP. 14 Basic science evidence includes likely identity of the supraspinal source, particular pathways, spinal cord sites, as well as nerve cell receptors and neurotransmitters involved in the sensory, behavioural and other responses seen with both animal and human subjects. 15

Human studies, involving normal and lateral epicondylitis subjects, indicate that large diameter joint afferent stimulation arouses a descending inhibitory system thought to originate in the lateral peri-aqueductal grey matter of the brainstem. 15 This system exerts segmental postsynaptic inhibition on dorsal horn pain pathway neurones. In animal studies, antagonists to a range of transmitter candidates implicate descending pathways which use serotonin acting at 5HT 1A and noradrenaline at α 2 -adrenergic spinal cord receptors in achieving this effect. 13 Moreover, this combination may be unique to mechanical stimuli/MP. Inhibitory products (opioids, GABA) and their receptors known to be associated with other types of stimulation therapy (e.g. TENS) were eliminated from this process. 13 Also recently, Malisza et al. 16,17 used functional magnetic resonance imaging (fMRI) to demonstrate a trend towards reduced activity in ‘pain relevant’ areas of the spinal cord and brain of animals following passive movements to their knee joints. Obviously, this work needs to be extended to various groups of normal and clinical human subjects.

Collectively, these studies are forming an impressive body of neurological mechanisms based research. Moreover, (collaborative) involvement at the basic sciences level creates awareness of the direction and opportunities of related research. One result of this is that viable, appropriate (to MP) future investigations largely suggest themselves. The clinical relevance of such work to MP will be advanced by greater use of definable categories of patients, as well as MP interventions. Regardless of how a ‘stimulation’ role for MP might be perceived in some quarters, the initiatives, scientific and professional, taken by researchers in this field are an object lesson in research for the entire profession.

A word of caution, however, when it comes to the anatomical and physiological identity, and behavioural specificity, of stimulus aroused endogenous pain control systems in humans. For one thing, it is increasingly apparent from animal studies that recognised nervous system pathways together with the three major neurotransmitters/modulators involved, opioids, serotonin and noradrenalins, interact in a highly complicated and variable manner. Furthermore, brainstem nuclei of different origin can, via indirect pathways through the (rostral ventromedial) medulla, end up acting at the same receptors in the spinal cord. 18,19 Importantly, it is now evident that extensive anatomical, physiological and functional differences exist among certain experimentally preferred animal species (e.g. rat). As Proudfoot 20 pointed out, specific connections among and between supraspinal and spinal cord neurones, together with the functions they subserve, not only vary from species to species but also between different stocks and strains of the same species of animal.

Together, such differences and complexities help explain some of the variation in results from otherwise
methodologically similar studies. They also jeopardise selective extrapolation of such evidence for purposes of hypothesis formation and the interpretation of clinical observations in humans.\textsuperscript{18,21} Adamant interpretation is further compromised by the possibility that, for a number of reasons, humans may themselves exhibit individual and periodic variations in the functioning of their endogenous pain control systems.\textsuperscript{22–24}

**LEARNING AND MEMORY-RELATED MECHANISMS**

*Therapeutic 1 – Habituation*

The aim and clinical implications of (passive) movement-mediated arousal of an endogenous pain control system are, of course, precisely the same as for any other 'stimulation' therapy (e.g. TENS). Namely, palliation with perhaps amelioration of muscular impediments to active movement thereby facilitating the return to normal function. Certainly, within physiotherapy circles, no other claim or role for stimulation mediated (temporary) pain relief has been made or implied with respect to MP. However, it is reasonable that many clinicians expect (and will only willingly accept!) a more enduring mechanism, neurological or otherwise, for the effects of their clinical ministrations.

Though somewhat vague, the proposal that progressive mechanical stimulation (e.g. ‘graded’ mobilisation) promotes stimulus tolerance and functional restoration by effectively ‘desensitising’ the nervous system implies a more prolonged effect (e.g. Vlaeyen and Crombez).\textsuperscript{25} Thus, Stanton-Hicks et al.\textsuperscript{26} declared: ‘the process of desensitisation may involve both a pharmacological approach to reduce pain and a process of gentle controlled non-nociceptive stimulation using heat, massage, pressure, cold, vibration, movement etc., to help restore normal sensory processing’ (bold text mine). Isometric strengthening and ‘stress loading’ are subsequently introduced to help overcome physical and psychological barriers to active movement.\textsuperscript{26} Precisely how graduated exposure to therapeutic mechanical stimuli might assist the nervous system to adjust to everyday movement-related activity is not stipulated. Initially at least, arousal of endogenous inhibitory systems could well be part of this process.\textsuperscript{27}

Standard MP practice in such situations would entail the initial performance of passive movements in some uninvolved pain-free direction and/or angle (‘range’). ‘Progression’ towards more pathologically involved movements is timed to follow sufficient repair and the gradual subsidence of sensory and motor responses (e.g. Maitland et al.\textsuperscript{3}). Again, neurologically, this is a typical desensitisation process and one whose success might partly depend on a contribution from (descending) pain inhibitory systems. However, a more ‘persistent’ explanation of what may be occurring clinically in these situations comes from central learning theory and its mechanisms. The first of these likely to be of relevance is a form of non-associative learning termed habituation.

Habituation is defined as a type of synaptic ‘learning’ that leads to decreased behavioural responses to repeated stimulation.\textsuperscript{29} Though the actual reason why is unclear, the mechanism involves a progressive and continuing decline in efficacy of Ca\textsuperscript{2+} channels on the presynaptic nerve terminal following repeated opening. Adequate Ca\textsuperscript{2+} influx is necessary for the release of quanta of neurotransmitter substances. Diminishing neurotransmitter results in a progressive decrease in the size of the postsynaptic potential (nerve impulses). Ideally, in the clinical situation this would be reflected in positive changes in subjective experience (pain) and associated motor responses.

Thus, Harman\textsuperscript{29} speculated that habituation may be a means whereby therapeutic sensory input ‘competes’ successfully with pain sensitisation, thereby helping restore an otherwise sensitive nervous system to normal. In learning theory terms, this would be the situation when the nervous system elects to eliminate neural activity it decides, for whatever reason, has no further meaning (and replace it with that which does). The result clinically would include, for one thing, the return to ‘normal sensory processing’ of large diameter A\textsubscript{β} mechanoreceptive afferent input.\textsuperscript{30} Harman\textsuperscript{29} does stress, however, the importance of duration – relatively lengthy or repeated periods of therapeutic stimulation (see Jull and Moore).\textsuperscript{31} Together, this is offered as a reason for tolerance to acutely employed interventions such as continuous passive motion devices.\textsuperscript{29,32}

Relatively prolonged (1 h or more) repetitive mechanical (and electrical) stimulation has been used more or less successfully for pain management with the major pathology limb amputation.\textsuperscript{33,34} In addition, these studies reported interesting before and after relationships between pain and imaged (fMRI) changes such as an expanded cortical representation has also been seen with musculoskeletal conditions such as (chronic) low back pain.\textsuperscript{35} Recently, improvement in (hand) muscle dystonias was shown to follow increasing duration (up to 2 h daily) of therapeutic active movement.\textsuperscript{36} The intervention, named ‘sensory motor retuning’, helped overcome painful involuntary muscle contractions and their disabling consequences. It might be noted that the abnormal postures and movements characteristic of these disorders are highly task and direction specific. Significant correlations were also
found between treatment, clinical resolution of dystonia, and imaged reversal of the formerly ‘degraded’ somatosensory cortical map.\textsuperscript{37}

The fact that abnormal cortical representation may be reversed with appropriate peripheral stimulation has led Sandkühler\textsuperscript{38} to conclude that these cases are a form of ‘transient functional (nervous system) plasticity’, and not some more permanent change in structural wiring. The phenomenon of ‘learned’ changes in central nervous system function, or plasticity, has become an increasingly important focus of pain mechanisms and its management. Evidence is accumulating, from behavioural to biological, that noxious stimuli/tissue damage produces ‘learning-type’ changes at the first pain pathway synapse in the spinal cord.\textsuperscript{39} Central nervous system ‘plasticity’, in this case the relationship between pain mechanisms and those of learning and memory, is clearly of symptomatic significance to clinicians. It is, therefore, appropriate to discuss first synaptic events associated with central nervous system plasticity in terms of the production and maintenance of pain. However, as will then be argued, certain of the evidence is also relevant to neurologically based therapeutic mechanisms for sustained clinical efficacy with MP.

Production of pain

Several characteristics of (associative) learning and memory formation make this a suitable context within which to discuss current understanding of pain mechanisms.

Learning and the formation of ‘memories’ in general are believed to involve an activity-dependent enhancement of synaptic efficacy known as long-term potentiation (LTP).\textsuperscript{40} Long-term potentiation continues to be the topic of intensive study in such memory-related areas of the brain as the hippocampus and cerebellum. Put simply, LTP is the process whereby a suitably produced barrage of impulses in the presynaptic neurone causes lingering, chemically mediated physiological and structural changes in the postsynaptic neurone. As a result, the synapse (circuit) in question is rendered capable of ‘remembering’ or readily recalling the circumstances and consequences of its original activation. Thereafter, effectively infinitely less stimulation is required to evoke the same response. In other words, LTP is a potentially prolonged, memory-related form of central nervous system plasticity or ‘sensitisation’.

Spinal cord pain pathway neurones also undergo rapid sensitisation following a suitable barrage of peripheral nociceptive afferent input, the phenomenon of ‘central sensitisation’.\textsuperscript{41} Central sensitisation is known to make a significant contribution to clinically observed symptoms and signs.\textsuperscript{30,42,43} It is becoming increasingly clear that many of the mechanisms known to be responsible for activity-dependent sensitisation of dorsal horn pain pathway neurones closely resemble those associated with supraspinal memory-encoding LTP.\textsuperscript{38,39} Indeed, there is sufficient similarity, supported by electrophysiological, biochemical and behavioural evidence, to nominate this variety of LTP as the molecular basis for not only acute, but also chronic continuous or relapsing clinical pain and disability. It is essentially this basis and its potential that underlie the following quote from Carr and Goudas\textsuperscript{44}:

‘…the biological and psychological foundation for long-term persistent pain is in place within hours of injury’.

Though there is not yet complete agreement,\textsuperscript{45} several lines of investigation endorse the proposal that central sensitisation is a spinal cord form of LTP. In addition to the production (and maintenance) of pain/hyperalgesia, these studies demonstrate commonality with respect to such features as means of induction, cellular mechanisms and pharmacological profile. For example, long-term excitation/potentiation of C fibre-evoked dorsal horn field potentials\textsuperscript{46} and responses of single wide dynamic range neurones\textsuperscript{47,48} has been demonstrated following intense electrical and ‘natural’ (tissue damaging) stimuli. These lingering changes are NMDA (glutamate) receptor dependent,\textsuperscript{46,48–51} and involve the intracellular influx/internal release of calcium\textsuperscript{52} with subsequent activation of protein kinases.\textsuperscript{52–54} Recently, Zhang et al.\textsuperscript{55} demonstrated that brief tetanic sciatic nerve stimulation produced behavioural responses (paw withdrawal incidence, latency) to mechanical and thermal stimuli that lasted for about one week. Moreover, these responses along with central sensitisation/LTP induction could be prevented by administration of the ‘non-competitive’ NMDA receptor antagonist MK-801 30 min prior to stimulation.\textsuperscript{55}

It should be noted that, unlike the hippocampus which uses only glutamate receptors, spinal cord LTP also requires activation of neurokinin receptors (e.g. NK1 – substance P\textsuperscript{50}). On the other hand, there is recent evidence for the presence of two fundamental features of hippocampal learning-memory related LTP at the spinal cord. Calcium-calmodulin-dependent protein kinase II (CaMKII)\textsuperscript{56} and late-phase protein synthesis dependency\textsuperscript{57} have been shown to be ‘crucially’ involved in noxiously induced sensitisation of spinothalamic neurones. The expression of CaMKII was significantly increased by 15 min and its phosphorylation by 5 min following intradermal injection of capsaicin.\textsuperscript{57} Administration of protein synthesis inhibitors to local spinal cord segments
30 min before tetanic sciatic nerve stimulation caused a progressive decline in late-phase LTP of C-fibre evoked dorsal horn field potentials. These potentials fell to prestimulus values by 270 min post-stimulation. This is in stark contrast to ‘control’ conditions where elevated levels, due to new protein synthesis, remain unchanged for at least 10 h (end of experiment).52,57

Importantly, (auto)phosphorylated CaMKII is now known to have more than just a modulatory role on impulse transmission (increased conductance due to phosphorylation of AMPA channels). It also ‘drives’ processes that alter the actual structure of synapses.40,58,59 Synaptic enlargement, involving both pre- (e.g., increase in the number of transmitter release sites) and post- (e.g., insertion of more AMPA receptors/channels into the cell membrane) synaptic events can be measured 2 h after the induction of supraspinal LTP.60–62 Recent evidence demonstrates that LTP-induced synaptic growth involves a significant increase in the number, and size (2-fold), of actin-rich dendritic spines.63 These small modifiable protrusions on dendrites are the major sites of synaptic contact. Larger synapses and contact sites presumably mean more AMPA channels.64 This then is further indirect endorsement that increased transmission and synapse size following LTP are associated with an increase in the number of postsynaptic AMPA receptors/ion channels.40,65,66 It is reasonable to expect that similar structural changes will also be demonstrated at spinal cord (and supraspinal) pain pathway synapses.

Thus, synaptic responses may be magnified and prolonged through activity-dependent physiological modulation and anatomical modifications that are potentially permanent. Moreover, it appears that natural learning ‘strengthens’ synapses in the same ways and by the same processes that mediate LTP.57 There is no reason to assume that this would not include central synaptic ‘learning’ due to pain. Hence, it is easy to concur with Lisman’s40 comment that activity-dependent synaptic modification associated with LTP is likely to have extensive ‘behaviourally meaningful’ consequences.

The clinical significance of nociceptor ‘activity’-dependent spinal cord (supraspinal) LTP to MP is fairly obvious. It would constitute not only a molecular mechanism for acute pain and its consequences, but also a potentially lasting physiologically and structurally mediated ‘memory’ basis for chronic continuous, or relapsing, pain and associated disability. The costly and distressing clinical picture this raises is all too familiar to purveyors of MP, which is often prescribed for the attempted management of such cases. This being so, it becomes necessary to think beyond the periphery, with its hypomobile (‘stiff’)

joints and ‘wasted’ muscles, for causal mechanisms. ‘Activity’ (pain) induced changes in central nervous system synaptic structure and function, that form relatively rapidly and linger, would also need to be considered. Assuming, with at least some cases, such nervous system changes are a potent factor clinically, an important issue then becomes how these ‘memories’ could be overcome by MP interventions. What might be the mechanism(s) whereby a peripheral movement based intervention turns neurologically and behaviourally entrenched, maladaptive postures and movement patterns into functionally useful motor behaviour? Again, learning theory and memory mechanisms may provide an answer to these questions. Specifically, several features of the behavioural and neural mechanisms for what are known as ‘aversive memory acquisition and its extinction’ appear particularly relevant in this regard.68

**Therapeutic 2 – Extinction**

Typically, aversive memory acquisition experiments involve the production and assessment of a motor (e.g., escape, ‘freezing’, avoidance) and, presumably, affective response to a painful stimulus (e.g., electric shock).68,69 The parallels with peripheral tissue insult and its behavioural consequences are self-evident. Repeating the painful process re-inforces the motor response, but then so does simply the threat of the unwanted stimulus – expectation of pain. Extensive investigation has identified such factors as induction variables (‘cueing’, ‘context’), brain areas concerned (e.g., amygdala, hippocampus), as well as the central nervous system receptors, transmitters and enzymes involved.68,70–72

A speculative extrapolation to the clinical situation would see the injured/painful area protected (i.e., ‘guarded’ or inhibited) at times and for a variety of reasons excessively. However, at some point, the patient is in need of at least minimal movement. In fact, it may well be the more physically and mentally ‘trained’, or stoical, individual who puts forth the greatest effort under these circumstances. Whatever the case, an otherwise ‘unnatural’ pattern of limb or trunk position, posture or gait is quickly contrived by the nervous system. Both the relative ‘success’ for compliance, along with the provocation of greater pain (hyperalgesia) by deviation from these albeit awkward movement patterns, results in their synaptic ‘strengthening’ and functional dominance (LTP). Significantly, such (mal)adaptive synaptic memory formation is strongly influenced by peripheral sensory input, nociceptive and proprioceptive. Evidently, a ‘reasoning’ nervous system has little difficulty in
also arriving at the same end-point by simply anticipating the likely painful consequences.

All such contrived changes, behavioural and neurological, are meant to be, and usually are, temporary. As the pain-generating pathology subsides, pain declines and normal motor behaviour again takes over. However, while primary physical sequelae are generally few, it is important to appreciate that the nervous system has now acquired a protective (pain) ‘memory’, albeit at this stage one that is suppressed.\(^{22,72–75}\) Besides further tissue insult, circumstances under which ‘latent’ memories and their physical manifestations might reappear are presently imprecisely understood. However, at least in some instances, there may be overlap with known risk factors for periodic relapse or chronicity of clinical pain syndromes. These factors include the nature and extent of the original pathology, early pain severity and a range of environmental and psychological factors.\(^{76–79}\)

Alternatively, should the initially ‘helpful’ changes and associated motor behaviour persist for any reason, these can become highly maladaptive secondary sources of chronic symptoms and disability.\(^{80}\) Secondary sources of pain may succeed (?sustain) the primary pathology and serve not only to prolong the behavioural (motor) responses, but also to re-inforce and sustain (mal)adaptive central synaptic changes. As stated above, several entities identified as risk factors for continuous or relapsing pain and disability could compound such events. Whatever the cause, it is fortunate that suitably indicated and administered MP interventions are proving to be a sound and relatively successful physical approach to the rehabilitation of such patients.

‘Movement control’ and extinction learning

The interventions in question include the translation of peripheral anatomical and biomechanical observations, into applied principles of motor learning and motor ‘control’.\(^{81}\) Specific therapeutic objectives include the provision of stability for vulnerable (joint) structures,\(^{82,84}\) and the correction of maladaptively retained habits of joint ‘loading’ and active movement by the substitution of suitable adaptive motor patterns.\(^{80}\) The aim is to thereby facilitate engagement in everyday activities in a progressively functional and pain-free manner. Thus, together with other beneficial consequences, patients are effectively provided with strategies for engaging in occupational and other physical activities (the aversive enterprise) without provoking pain (the ‘fearful/unsought result). This principle of ‘exposure without danger’ is fundamental to various interventions employed in the extinction of aversive memories.\(^{68,70,71}\) In this way, learning theory is proposed to provide a neurological model which helps account for relatively sustained efficacy with (active) movement-based MP interventions. Namely, behavioural and neural mechanisms associated with the ‘extinction’ of noxiously acquired ‘memories’ and their maladaptive motor and other consequences.

The present contention is that the process of extinction of aversive memories readily lends itself to neurological mechanisms of clinical MP. Teaching the nervous system (not muscles!) to instruct muscles on how to negotiate everyday movements without (undue) pain provocation, results in the laying down of a ‘new’ adaptive motor ‘memory’ – that of extinction. This process also involves activity-dependent physiological and anatomical changes at synapses, in other words LTP (just as occurred with former noxiously acquired maladaptive motor patterns). It is interesting that the tendency for common musculoskeletal conditions to relapse periodically also conforms with a fundamental principle of memory acquisition and extinction. Namely, with appropriate training and practice, memory for extinction assumes dominance, suppressing that responsible for the expression of the former maladaptive sensory-motor response. However, the latter is not totally erased; under certain circumstances, it has the potential for either ‘spontaneous recovery’ or ‘renewal’.\(^{35,86}\) It goes without saying that the cause of relapse clinically may be a further traumatic episode. Even so, ‘latent memory’ could also be a factor in the well-known tendency for relapse with common musculoskeletal disorders such as back pain where the trigger for reappearance is disputed or seemingly trivial.\(^{86,87}\)

As Myers and Davis\(^{68}\) have emphasised, extinction is a new learning process accompanied by its own nervous system ‘plasticity’. It is not simply a reversal of that associated with the former maladaptive memory. Nevertheless, at the macro-level many of the same brain structures and circuits appear to be engaged.\(^{68,72,75}\) At the molecular level, both ‘memories’ probably utilise a number of the same, as well as separate, intracellular ‘signalling’ pathways (e.g. PKA, MAPK, CaMKII).\(^{58,88}\) In addition to modulatory functions, these enzymes initiate gene transcription and protein synthesis which create the long-term changes in synaptic structure.\(^{89,90}\) When it comes to their respective expression, however, a crucial difference between acquisition and extinction appears to lie not so much with the cells contacted but with the specific receptors and neurotransmitters involved. These are thought to constitute GABA for extinction (inhibitory) as opposed to glutamate for acquisition (excitatory).\(^{68,88,91}\)

It is worth noting that extinction memory has additional features contributing to its classification as a lingering form of learned or conditioned inhibition,
which are compatible with clinical MP. For instance, it is usually agreed that (procedural) learning and memory in general benefit from what is known as a spaced or distributed method of training.\textsuperscript{92–94} In motor learning terms, this includes providing precise instruction, but on a carefully measured basis that allows for controlled practice and the absorption of constructive extrinsic feedback (knowledge of results). The melding of this information with actively acquired intrinsic (proprioceptive) feedback is deemed especially important in the early, conscious or ‘cognitive’ phase of motor learning.\textsuperscript{95} Moreover, in the final so-called autonomous phase, periodic ‘top-ups’ are considered useful, even necessary.\textsuperscript{94}

Clinical practice similarly involves the delivery of an MP intervention on a periodic or ‘distributed’ basis (e.g. ‘x’ times per week). Learning theory would endorse ‘consolidation’ intervals between ‘training’/treatments as having a number of potentially beneficial attributes. These include transferring the consequences of accurate information, and practice-generated (relatively pain free) proprioceptive feedback, to long-term memory stores. It will be recalled that this process which involves the manufacture, delivery and appropriate laying down of new protein, is characteristic of late-phase NMDA-dependent LTP.\textsuperscript{95,96} There is now compelling evidence that the manufacture and synaptic ‘capture’ of new protein is essential for learning and memory retention.\textsuperscript{40,59} To complete the circle, protein synthesis dependency, characteristic of the late phase of NMDA-dependent LTP, is also a fundamental feature of learned extinction of aversively (pain) acquired memories.\textsuperscript{68,75,88,90}

Given the above (and probably endorsed by clinical experience), evidence that the effects of sessional extinction training can also be ‘strengthened’ by repetition should come as no surprise. In clinical terms, this would mean ensuring that details about new, relatively pain-free motor training patterns are patiently delivered, carefully monitored and thoroughly absorbed by patients. In some instances, this (repetitious) process may need to be carried to the point of ‘overtraining’.\textsuperscript{73} Indeed, beneficial effects of such an approach could well extend beyond that of the immediate therapeutic goal. There is the additional possibility that deliberately fortified extinction might also influence the frequency of relapse with susceptible syndromes (e.g. back pain, see below). All of which becomes especially relevant when it is recalled that a history of past pain episodes (‘pain memory’) is a potient risk factor for chronic pain-related disability.\textsuperscript{55,97}

The evidence presented suggests that the clinical picture is potentially influenced by two opposing long-term memory traces which ‘compete for control of behaviour’.\textsuperscript{73} Relapsing pain and its consequences may, therefore, be seen as a periodic breakthrough (for a variety of reasons) of the less desirable of these ‘memories’.\textsuperscript{68,72} In ‘competitive’ terms, Eisenberg \textit{et al.}\textsuperscript{73} have shown that increasing the number of extinction training sessions (from 1 to 10) resulted in ‘massive extinction’. The inference is that this would improve the likelihood of the therapeutically desirable memory, extinction, retaining or readily regaining ‘appreciable control of behaviour’.\textsuperscript{73} Findings of this nature imply that it would be sensible to engage, albeit judiciously, in treatment strategies that could positively influence the desired response, in this case the dominant expression of extinction. As indicated, appropriate tactics might include controlled delivery of treatment (see above), a degree of ‘overtraining’ of learned pain free routines, and the introduction of late periodic revision or ‘top-ups’. Further findings of these and other researchers point to such precautions being particularly relevant where initial pain intensity (pathology) is especially severe.\textsuperscript{78}

Before concluding it is worth mentioning a further ‘competitive’ issue of potential relevance to clinical MP, one involving the well known variable selective attention. Clearly, a logical counter to the known negative effects of excessive attention to pain and/or body area (hypervigilance) is distraction (see Hasenbring\textsuperscript{102–101}). Thus, experimentally, the subject is asked to shift attention away from a noxious stimulus and onto some more pleasant or ‘neutral’ input. Bushnell \textit{et al.}\textsuperscript{103} were adamant that the therapeutic benefit of such an enterprise does not derive from simply ignoring the pain. Rather, as endorsed by fMRI, the effect is to shut down activity in the so-called supraspinal pain ‘matrix’ – anterior cingulate cortex, insula, thalamus, cerebellum. Presumably this is achieved by (cognitive) arousal of endogenous pain inhibitory system(s).\textsuperscript{103} However, under ‘real’ circumstances such non-specific shifts of attention or distraction are not always easy for patients to achieve. This has been shown to be especially so for pain-fearful individuals who appear relatively incapable of conscious orientation away from pain (e.g. Keogh \textit{et al.}\textsuperscript{99} and Delghani \textit{et al.}\textsuperscript{104}).

In an interesting twist to this strategy, Longe \textit{et al.}\textsuperscript{105} administered thermal pain and a pain inhibitory intervention, vibration, concurrently, and asked subjects to direct their attention to one or the other (or to a neutral stimulus). Again, backed by imaged alterations of activity in the pain ‘matrix’, it was found that, despite receiving treatment, both imaged neural activity and the sensory experience increased when the focus was on pain. Moreover, these decreased only when attention was directed towards the therapeutic intervention. This is an extraordinary finding! It implies that the ability of a neurologically attested therapeutic stimulus to suppress nociceptive input
(see Melzack and Wall\textsuperscript{106}) could be compromised by an entirely independent factor – selective attention.

On the positive side, however, it does suggest a mechanism for explaining, as well as a means of assisting, the ‘dominance’ of extinction memory from a clinically competitive perspective. It might be noted that the evidence is also compatible with an abiding principle of habituation learning. Namely, the therapeutic stimulus is induced to assume, and pain lose, its ‘meaning’ and so conscious awareness. It is reasonable to presume that positively inclined (‘expectant’) patients probably do tend to concentrate their attention on the therapeutic ‘stimulus’ (e.g. passive/active movement). Nevertheless, it seems that it would not hurt (sic) for clinicians to actively encourage this choice!

To summarise, sensory input – nociceptive and proprioceptive – produced as a result of peripheral tissue insult leads to physiological and anatomical changes at synapses in the central nervous system, a form of LTP. As well as for pain, these synaptic events are a learned mechanism for the expression of (mal)adaptive changes in motor function – muscle tone, and postures and movements collectively known as ‘behaviour’. Unless and until movement can be carried out in the relative/total absence of pain, both the synaptic ‘memory’ and its behavioural consequences are likely to be self-reinforcing. Indeed, they have the potential to become chronic. This is generally averted by a combination of natural history and delivery of appropriate therapeutic interventions. An important neurological consequence of the latter is to drastically change – that is ‘normalise’ – the pattern of sensory input.

Natural history may sometimes be thwarted or overridden by, for example, the unintended creation of secondary ‘mechanical’ sources of pain and functional impairment. The nociceptive and proprioceptive input so produced is likely to be interpreted by the nervous system as an ongoing, similarly threatening situation. In any event, the fundamental aim of MP is to facilitate the performance of functionally appropriate, relatively pain-free movements. Successful execution not only substantially eliminates nociception, it also results in an entirely different pattern of proprioceptive input. Together this would go a considerable way towards ‘normalising’ central sensory processing as advocated by authors such as Stanton-Hicks \textit{et al.}\textsuperscript{26} and Vlaeyen and Crombez.\textsuperscript{25} Furthermore, recent research supports the proposal that providing patients with suitable information assists in reducing the threat or fear factor of (any remaining) pain.\textsuperscript{107,108} Though assumed, peripheral structurally based mechanisms for achieving this therapeutic goal with MP have yet to be demonstrated unequivocally.

Recently, Souvlis \textit{et al.}\textsuperscript{109} reported an increase in baseline thresholds for spontaneous and mechanically provoked epicondylitis pain following six alternate day treatments with a non-noxious passive movement manoeuvre (‘grade III’). This ‘technique’ has been used extensively to investigate stimulus-induced arousal of descending pain inhibitory systems.\textsuperscript{14,15} No other mechanistic claim has been made by these authors, and it is far from clear whether the limited treatment involved would have a worthwhile influence on the pathology of chronic epicondylitis. Any such effect may be, in part, an indirect consequence of temporarily reducing movement (e.g. grip) related pain. This would also ‘set the scene’ for the extinction of aversely acquired pain pathway plasticity. Further investigation is needed in order to clarify the ‘cumulative’ effect for repeated ‘grade III’ treatments observed in this study.\textsuperscript{109}

**CONCLUSIONS**

Three neurological mechanisms for the clinical efficacy of MP have been presented: (i) arousal of endogenous pain inhibitory systems; (ii) habituation; and (iii) (aversive memory) extinction. Of these, the first is evidence-based but of limited duration. Though currently hypothetical with respect to MP, the other two are likely to be much longer lasting. A caveat is that both would probably benefit from somewhat extended periods of stimulation or ‘training’.

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