Introduction

Low back pain (LBP) constitutes a major public health problem in Westernised societies. Recent research has shown that the total healthcare costs of CLBP patients is approximately double those of matched controls [1], and that CLBP is the single greatest cause of global disability [2]. Whilst estimates may vary considerably, there is no doubt that the financial impact of low back pain is significant and growing [3]. The clinical course of LBP is highly variable, with 3-10% of patients known to develop chronicity [4], defined as LBP which persists for 3 months or more [5]. Many CLBP management strategies have been proposed and trialled (including pharmacological, interventional, and surgical approaches), but have at best achieved moderate success [6]. It can be argued that to date healthcare strategies have focused too extensively on 'structural correction' [7], and that traditional manual therapies have, until relatively recently, been too impairment-orientated [4, 7].

Cortical remapping (CR), defined as neuronal reorganisation within the higher centres of the brain, secondary to cortical neuroplasticity, is a common feature of many chronic pain states [8] and has more recently been documented in CLBP [9]. Extensive CR has been identified in areas known to be involved in pain processing ('the pain neuromatrix') [10], somatosensation [11] and motor planning [12]. Brain imaging studies in CLBP patients have demonstrated significant changes in neurochemical profile [13], neuroanatomy [14,15], cortical representation [11], and cortical responsiveness [16], with the magnitude of change seen to be proportional to symptom chronicity and the level of associated depression or anxiety [13,16].

Whether these changes are cause or effect in CLBP has yet to be established, however, there is growing opinion that maladaptive neuroplastic changes within the central nervous system may play an important role in symptom generation and perpetuation in CLBP [9].

Several treatments have evolved which specifically target normalisation of cortical remapping. These include mirror-box or mirror visual feedback (MVF) therapies [17], graded motor imagery (GMI) [18], and sensory discrimination retraining (SDR) [19]. MVF and GMI both involve progression through a graded motor recruitment program, whilst visual feedback of the unaffected, contralateral limb or body part is provided using mirrors [17]. Participants begin with basic motor imagery, such as recognition of limb laterality and imagined movements, and progress to more complex motor functions as symptoms allow. SDR targets an improvement in sensory acuity using various techniques such as two-point discrimination (TPD) or/and character recognition (Graphesthesia) [20]. All have been applied in the management of other chronic pain states including complex regional pain syndrome (CRPS) and phantom limb pain (PLP) with varying degrees of success [20-22].

Since there is growing evidence regarding the importance of cortical remapping in CLBP [8, 9, 11], it is reasonable to consider these treatment approaches in the management of the condition. However, the strength of evidence regarding their effectiveness in this patient population is unclear at this time. Two single case

studies [23, 24] have reported encouraging results using cortical remapping techniques and emphasise the need for further, high quality research in this area. The aim of this systematic review was to assess the current evidence regarding the effectiveness of treatment modalities which specifically target cortical reorganisation in the management of CLBP.

METHODS

Data sources and search

A comprehensive online search was performed using Medline/Pubmed, OVID, EMBASE, Allied and Complementary Medicine (AMED), Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsychInfo, Physiotherapy Evidence Database (PEDro), British Nursing Index (BNI), Cochrane Library, and Healthcare Management Information Consortium (HMIC). The OVID platform was used to search AMED, EMBASE, HMIC, Medline, and PsycInfo, EBSCO for CINAHL, and ProQuest for BNI. Search strategies were developed using a standardised Population/Intervention/Comparison/Outcome (PICO) format [25]. Electronic searches were performed using both single, key search criteria, and combination searches using Boolean operators, from the inception date of each database to September 2013. Preliminary research had suggested that the number of articles matching key search parameters was likely to be small, so all multiple participant

study designs were included, and no language restrictions were used. Key search terms are summarised in Figure 1.

Eligibility criteria

The following inclusion/exclusion criteria were applied to retrieved records:

1) Subject population: Chronic low back pain.
2) Interventions: graded motor imagery, mirror visual feedback therapy, sensory discrimination retraining and/or tone pitch recognition, including their derivatives and combination protocols.
3) Interventions compared with relevant 'current practice' intervention (controlled trials only)
4) Primary outcome measures: pain, disability and relevant cortical imaging measures.
5) Studies written in English (or English translation available)
6) Animal model studies and unpublished studies were not considered.

Full text copies of the remaining eligible articles were obtained, and the same screening repeated to optimise relevance. Snowballing from the bibliographies of the final articles selected for inclusion in this paper was then applied.

Data Extraction and analysis

Data extraction was independently performed by two reviewers (PD and SP) using a standardised data extraction proforma. Any differences of opinion were resolved by consensus. Attempts were made to contact the primary author of any studies where data supplied in the original publication was deemed to be incomplete or insufficient. A qualitative synthesis of methodological quality of each article was performed by the principal reviewer (PD) using the appropriate Critical Appraisal Skills Programme (CASP) criteria [26]. This was reviewed and corroborated by a second, independent reviewer (SP). A comprehensive analysis of risk of bias and study limitations is included in the discussion section of this paper.

RESULTS

Study selection

Initial electronic database searches identified 10 potentially relevant publications, with the addition of an 11th via manual bibliography screening. Three were subsequently eliminated following screening of abstracts, and a further 3 on screening of full text articles, leaving 5 for inclusion in this review. The appropriateness of final article selection was corroborated by a second, independent assessor (SP). Figure 2 depicts a flow-diagram summarizing the screening process used to select eligible articles for inclusion in this review [27].

Results of individual studies

The 5 articles included in this review comprised 3 single-blind RCTs [28-30]; a randomised single cohort cross-over trial [31] and a multiple case study design [32]. Key characteristics and principal findings are summarised in Table 1.

Sensory Discrimination Retraining (SDR)

Two studies examined the effect of SDR on CLBP outcomes [28, 29]. Barker et al [28] compared the effects of SDR using a FairMed device with a course of conventional TENS (8hz/100μs). The authors report no significant difference ($p<0.05$) in pain, physical and emotional function scores (measured using VAS, ODI, and HADS respectively) at 12 weeks after treatment. Morone et al [29] compared SDR retraining using perceptive rehabilitation (PR) with a back school intervention group, and a control group (who received pharmacological intervention only). PR involved subjects performing a series of perception tasks while lying supine on their Surface for Perceptive Rehabilitation tool (comprised of a series of deformable cones). They demonstrated a significant reduction in VAS pain outcomes in both intervention groups ($p<0.001$), but also in their control group ($p=0.028$) with improvements maintained at 24 weeks. Pain improvements occurred more rapidly in the PR group, with the observed reduction in VAS pain outcomes immediately following intervention significantly lower than those for both the back school and the control group (specific p-values not reported). Oswestry Disability Index (ODI) scores improved significantly in the PR and back school groups (both $p<0.001$) but not in the

control group (p=0.734). There were no significant differences between the three groups immediately following intervention (p=0.403). However, the back school group demonstrated a significant improvement versus controls at 12 and 24 weeks (p=0.003 and p=0.008 respectively) [29]. There were no differences between PR and back school ODI scores at 12 and 24 weeks (p=0.065 and 0.169 respectively).

Mirror Visual Feedback

Wand et al [31] showed that visualisation of the lumbar spine (using mirrors) during repeated lumbar movements (10 repetitions of lumbar flexion, extension and both lateral flexions) significantly reduced pain levels immediately post exercise (mean VAS difference 9.3mm, 95% CI: 2.8-15.7, p=0.007). The duration of low back pain elicited was also shown to be significantly reduced with visualisation (mean difference in 'time-to-ease' 49.9s, 95% CI: 19.3-80.6, p=0.003). Analysis showed that the order of intervention (i.e. movements performed with or without mirror feedback) had no significant impact on all measured outcomes.

Motor control exercise

Tsao et al [30] demonstrated that 2 weeks of specific motor control retraining produced a corrective medial shift in Transversus Abdominus (TrA) primary motor cortex (M1) representation in CLBP participants ($p<0.016$), towards the 'normal' M1 locus previously observed in healthy participants [12]. No corresponding changes were noted in the control (self-paced walking) group ($p>0.57$). When all participants

were included in analysis, earlier postural recruitment of TrA was found to be moderately correlated with normalisation of motor cortex representation (r^2<0.12, p<0.044), this being more marked in the motor training group. The stability of these changes is unclear as there was no follow-up beyond the 2 week intervention period.

Combination Treatment Approach

Wand et al [32] used a multi-dimensional treatment protocol (termed sensorimotor retraining (SMR)), which combined elements of GMI, SDR, motor control exercise and MVF therapies. All 3 participants demonstrated an improvement in pain intensity, pain interference, and disability following 10 weeks of SMR and these improvements were maintained at 20 weeks follow-up. In addition, regression analysis identified significant trends between all outcomes and treatment phase (before, during and after) (all p≤0.01). One participant demonstrated a pre-treatment improvement in both pain and disability suggesting that the observed change may be attributable, at least in part, to natural recovery in this case.

Methodological considerations

Study design

Barker et al [28] employed a non-inferiority trial design. However, as they failed to include a control group, their results are vulnerable to 'assay sensitivity', and it is possible that they have incorrectly concluded 'non-inferiority' when the reverse is

173 true [33]. In addition, their standard comparison intervention, TENS, has been
174 shown to have questionable efficacy in the management of CLBP [35]. A
175 fundamental limitation of the study by Morone et al [29] is the omission of a
176 mechanism-targeted physiological outcome such as tactile discrimination, preventing
177 any conclusions being drawn concerning the neurophysiological mechanisms
178 underlying any treatment effect.

179

180 *Methodology*

181 A variety of recruitment strategies were used in these studies, from advertising in the
182 local paper [21] to convenience sampling from local primary and secondary care
183 referral sources [28, 29, 31]. All are a potential source of recruitment bias.
184 Demographic details were supplied for intervention subgroups in all studies, which
185 seem to suggest that participants were representative of the CLBP population.
186 However, as no between-group baseline analysis was reported by Barker et al [28],
187 significant differences between intervention subgroups cannot be excluded.
188 Randomisation of participants into intervention groups was reported in all 4 trials.
189 However, as Barker et al [28] did not attempt to conceal allocation, it is possible that
190 randomisation was compromised by prior knowledge of allocation.

191

192 Sample sizes were relatively small ranging from n=3 [32] to n=75 [29], with
193 intervention subgroup sizes varying from n=3 [32] to n=32 [28]. However, all studies
194 except Morone et al [29] provided a sample size calculation to justify this. All trials

employed single-blinding of assessors limiting detection bias, with double-blinding (of either subjects or therapists) practically very difficult to achieve in such interventional studies. A variety of outcome measures were used. All were appropriate and validated, ensuring robust internal validity. Detailed intervention protocols were included in all studies except for Morone et al [29], where insufficient detail was provided in the paper or subsequently, regarding their PR intervention protocol to allow future replication if desired. Attempts by the lead author (PD) to contact the research team to obtain the required data have been unsuccessful.

Data Analysis

Incorrectly applying parametric statistical analysis to non-parametric data can result in an overestimation of the significance of any treatment effect. Since Tsao et al [30] was the only study to confirm parametric status, and Morone et al [29] the only paper to state that they assumed their data to be non-parametric, it is possible that the clinical significance of any treatment effect has been exaggerated in the remaining trials [28, 31].

A potential limitation of all studies was incomplete intention-to-treat analysis (ITT). The aim of ITT analysis is to minimise the effects of non-random attrition of subjects (i.e. drop-outs) and thus maintain subgroups which are similar apart from random variation. It also controls for non-compliance and deviation from protocol by clinicians [34]. While all trials quoted the 'intention' of ITT analysis, it was unclear

whether the incomplete data sets from those participants who failed to complete the study protocol or follow-up were actually incorporated into the statistical analysis. Thus, there is a risk that the clinical effectiveness of the target intervention has been overestimated in these studies.

Interpretation

There are several factors which may contribute to reporting bias in these studies, and thus potentially compromise the accuracy and definitiveness of their conclusions.

1) No Confidence Interval (CI) inclusion. Only Wand et al [31, 32] quoted 95% confidence intervals for the mean difference with their statistical significance data.

2) Insufficient follow-up. Only Morone et al [29] employed a (relatively) long-term follow-up analysis in their trial (24 weeks), with follow-up in all other protocols limited to 12 weeks or less. It is therefore, impossible to assess the long-term effects and carry-over of treatment interventions.

3) Practicability of the treatment intervention. The ease with which any treatment intervention could be successfully used in an appropriate clinical setting, is of paramount importance to practice. Close inspection of treatment protocols used in these studies revealed a number of concerns. Barker et al [28] had significant problems with the durability of their device, with 20/32 subjects reporting a fault at some point in the intervention phase. Morone et al [29] did not describe their intervention in sufficient detail for replication. The treatment protocol employed

by Wand et al [32] was complex (incorporating components of GMI, MVF therapy and motor control exercise), making it difficult to estimate the relative effectiveness of the individual intervention components. In addition, applying such an intensive protocol to a very specific subset of musculoskeletal patients in a traditional clinical environment would inevitably lead to questions regarding cost-effectiveness. Thus, a multidisciplinary pain clinic setting might be considered a more appropriate venue for such interventions.

DISCUSSION

Summary of evidence

The findings of this review suggest that interventions which target cortical remapping (such as GMI, MVF, and SDR) have potential for application in the management of CLBP. Real-time lumbar visualisation using mirrors may significantly reduce the severity and duration of movement-associated low back pain [31], which correlates with previous findings in other chronic pain states such as CRPS [17]. There is evidence that motor control interventions can significantly influence M1 cortical representation and neuroplasticity, and appear to facilitate correction of pathological cortical mapping towards the agreed norm [30]. However, the mechanisms underlying this and the duration of any treatment effect in CLBP remain unclear. SMR has been shown to produce clinically significant short-term improvements in both pain and disability in CLBP subjects [32]. However, these results need to be

replicated in a larger trial to confirm statistical significance and longer-term benefit. Sensory discrimination retraining devices (Surface for Perceptive Rehabilitation and FairMed) were found to produce a significant improvement in both pain and disability [30] and 'be no worse than TENS' (in the management of CLBP), in Morone et al [30] and Barker et al [29] respectively, although both papers were found to be of low methodological quality.

Clinical Implications

The limited research that we have been able to identify which has examined the efficacy of these developing treatment approaches in CLBP is promising, particularly when taken in the context of the more extensive research findings in CRPS and PLP. The use of real-time visualisation of the spine using mirrors may facilitate significant short-term improvements in pain and disability in CLBP patients [31], but further longitudinal studies are required to establish the durability of these changes. Preliminary studies which have examined treatment protocols which target improvements in spinal tactile acuity are also encouraging [24, 29, 32]. However, while there is extensive research available on modalities of tactile acuity (TA) measurement in chronic pain, there is relatively little on TA treatment strategies (particularly in CLBP), and no accepted standardised treatment protocols.

Limitations of this review

Despite a comprehensive and systematic search strategy, only a very small number of articles were eligible for inclusion in this review. It is possible that limiting our search parameters to publications where English translations were available may have contributed to this. Another contributing factor to consider here is potential publication bias, where studies with negative results are less likely to be published [36].

The methodological quality of the 5 studies which were included was variable. All had some limitations, with the Barker and Morone et al papers deemed to be of low methodological quality. In addition, the heterogeneity of interventions employed made comparative analyses difficult.

Conclusions

The management of CLBP remains a considerable challenge to researchers and clinicians alike. There is substantial evidence regarding the important role of maladaptive cortical remapping in symptom generation and perpetuation in many chronic pain states including CLBP. Management strategies such as sensory discrimination retraining, graded motor imagery, and mirror visual feedback which specifically aim to drive adaptive cortical neuroplasticity to redress these changes have been shown to be effective in CRPS and PLP. This review has demonstrated the paucity of robust literature which has examined the efficacy of these treatment modalities in the management of CLBP. The results of the few studies which are available are encouraging. However, with variable methodological quality, small

sample sizes and no long term follow-up, it was not possible to draw any definitive conclusions as to the effectiveness of these modalities in CLBP. Further, robust research is therefore needed to investigate the considerable potential of these developing management approaches, to identify optimal treatment protocols and establish their long-term efficacy.

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