Sensory discrimination training for adults with chronic musculoskeletal pain: a systematic review

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ABSTRACT

Background: Sensory discrimination training (SDT) is a form of feedback guided sensory training used in the treatment of chronic musculoskeletal pain (CMP).

Objective: This systematic review aimed to investigate the efficacy and safety of SDT for CMP.

Methods: MEDLINE, CINAHL, EMBASE, AMED, CENTRAL, PsycINFO, Scopus, OT Seeker, PEDro, ETHOS, Web of Science, and Open Grey were searched for appropriate randomized controlled trials (RCTs). Included papers were assessed for risk of bias, and evidence was graded using the GRADE approach. The protocol was published on PROSPERO (CRD42018110796).

Results: Ten RCTs met the inclusion/exclusion criteria. There was conflicting evidence from seven RCTs for the efficacy of SDT for chronic low back pain (CLBP). There was very low-quality evidence from two studies supporting the efficacy of SDT for phantom limb pain (PLP). There was very low-quality evidence from one RCT for the efficacy of SDT for Fibromyalgia. No adverse effects of SDT were identified.

Conclusions: SDT has been delivered in multiple forms in the literature. SDT does not appear to be associated with any adverse effects and shows potential regarding its clinical efficacy. However, there is a lack of high-quality evidence upon which to make any firm clinical recommendations.

Keywords: Pain; sensory discrimination training; systematic review

INTRODUCTION

Chronic musculoskeletal pain (CMP) is a global healthcare problem affecting a fifth of adults worldwide (International Association for the Study of Pain, 2004). In the United Kingdom, it is estimated that 28 million adults live with chronic pain (Fayaz et al., 2016), costing over 2.1 billion for chronic low back pain (CLBP) alone (NICE, 2009). The economic cost of chronic pain is estimated at 3-10% of the gross domestic product (GDP) in the UK and wider Europe (Breivik, Eisenberg and O'Brien, 2013). CMP substantially impacts on all areas of functioning across physical, emotional and social domains (Baker et al., 2016; Karos, Williams, Meulders and Vlaeyen, 2018; Turk et al., 2008). It is not fully understood why some individuals develop CMP while others, with similar histories, do not. Studies have shown, however, that neuronal activity, in specific brain regions, differs between people with CMP and healthy controls (Diers et al., 2010; Kikkert et al., 2019; Lotze et al., 2001; Makin, Filippini et al., 2015; Makin, Scholz et al., 2015; Wand et al., 2011; Wrigley et al., 2009). Differences occurring in the somatosensory cortex - often referred to as cortical reorganisation, or disorganisation - have received particular attention. It has been proposed that alterations to the somatosensory cortex in people with pain may play a part in the development and/or maintenance of CMP (Andoh, Milde, Tsao and Flor, 2018; Kikkert, Johansen-Berg, Tracey and Makin, 2018; Mancini et al., 2019; Weiss, 2016). Conversely, the very neural plasticity that underlies the phenomenon of cortical reorganisation may facilitate the efficacy of specific, targeted, sensorimotor retraining treatments (Moseley and Flor, 2012) in which behaviourally relevant stimulation and training alters the somatosensory cortices (Robson and Gifford, 2013). It has also been reported, in healthy participants, training periods of at least 35 minutes daily, over five days improves both sensory and spatial discrimination ability (Weiss et al. 2007; Walter-

Walsh et al. 2009). As a result, a number of novel therapeutic approaches have been devised for the treatment of CMP based upon feedback guided sensory training. Such interventions include mirror therapy (Foell, Bekrater-Bodmann, Diers and Flor, 2014), sensorimotor retraining (Mueller et al., 2018), proprioceptive rehabilitation (Paolucci et al., 2016) and sensory discrimination training (SDT) (Flor, Denke, Schaefer and Grusser, 2001). These approaches all aim to trigger beneficial changes, at a cortical level, through reorganisation of the neuronal pathways underlying CMP.

SDT (of which there are many variations) involves the delivery of a particular, defined and controlled stimulus to the body, the recipient is then asked to make a judgement on an aspect of the stimuli (e.g. the location); feedback is then provided to the patient on the accuracy of their judgement (Flor, Denke, Schaefer and Grusser, 2001; Ryan, Harland, Drew and Martin, 2014). There is a growing body of evidence showing sensorimotor discrimination deficits in CMP conditions (a clinical signature of cortical reorganisation) provides a reasonable platform to suggest that retraining of these deficits through SDT may be a useful treatment approach for people with CMP (Catley et al., 2014). SDT has been applied to a variety of CMP conditions such as CLBP (Ryan, Harland, Drew and Martin, 2014), complex regional pain syndrome (CRPS) (Moseley and Wiech, 2009; Moseley, Zalucki and Wiech, 2008; Pleger et al., 2006; Pleger et al., 2005) and phantom limb pain (PLP) (Flor, Denke, Schaefer and Grusser, 2001).

Two systematic reviews (Daffada, Walsh, McCabe and Palmer, 2015; Kälin, Rausch-Osthoff and Bauer, 2016) have investigated the efficacy and safety of SDT for people with CLBP, but, to date, no systematic reviews have investigated the efficacy and safety of SDT in the wider adult CMP population. Such a systematic review is needed to guide clinical practice and direct future research in this field. Thus, the aim of this systematic review was to investigate the efficacy and safety of SDT for adults with CMP. This aim was met via the

following objectives:

1/ Systematic review of the literature in order to identify RCTS that have used SDT as an intervention for CMP conditions. 2/ Appraisal of the identified studies to assess their risk of methodological bias. 3/ Evaluate the efficacy of the intervention in a meta-analysis or presented as a narrative synthesis and identify any safety issues.

METHODS

Procedure

The Cochrane handbook for systematic reviews of interventions (Higgins and Green, 2011) was used to guide this work, and the review is reported in line with PRISMA guidelines (Moher et al., 2009). The review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (reference number CRD42018110796). The PICOS model was used to structure the systematic search and develop inclusion/exclusion criteria. Studies that included adults (18+) with chronic pain defined as 'pain without apparent biological value that has persisted beyond the normal tissue healing time, usually taken to be 3 months (International Association for the Study of Pain, 2003), were included. The review also considered studies where a strict ≥3months duration of pain has not been clearly stated within the inclusion criteria, but the chronic nature of the condition implied that participants' pain was of a persistent nature (e.g. osteoarthritis). The review considered studies that included participants diagnosed with CMP conditions such as CLBP, chronic neck pain, osteoarthritis or rheumatoid arthritis, in addition to those with widespread musculoskeletal pain.

Included studies had to have investigated SDT that met all three of the following criteria: (1) the initial delivery of a particular, defined and controlled stimulus (e.g. electrical or tactile) to

the patient's body, (2) the recipient makes a judgement on an aspect of the stimulus (e.g. the location) and (3) feedback is then provided to the recipient on the accuracy of their judgement, usually by a trainer/therapist. SDT requires the active participation of the patient, rather than simply the passive receipt of stimulation. Any form of SDT, in compliance with the operational definition above, was eligible for inclusion. The review included RCTs that; compared the intervention with no treatment (true control), usual care, or placebo, concomitant studies in which SDT was delivered in addition to another intervention (and that other intervention was received by both groups), *head-to-head* studies, in which SDT was compared to another active intervention. In addition, studies that compared one form of SDT to another were included in order to explore the evidence that efficacy may differ for different SDT protocols.

The primary outcome measure of interest was pain recorded using any valid and reliable outcome measures such as a visual analogue scale (VAS) or numerical rating scale (NRS) (Turk and Melzack, 2001). Secondary outcome measures were broad in nature and included any measures that evaluated health and well-being including, but not limited to, physical function, sensorimotor function, patient satisfaction, quality-of-life (QoL) and disease specific measures. Additionally, assessment of safety issues via adverse effects (AEs) reporting were included as an outcome of interest as they are important for clinical decision making (Loke, Price and Herxheimer, 2008).

Search Strategy

A search strategy was designed, with support from an information specialist, in keeping with the Cochrane collaborations' processes (Higgins and Green, 2011). To ensure a thorough search, large databases and subject specific databases were used (Bettany-Saltikov, 2010; Dickersin, Scherer and Lefebvre, 1994; Lefebvre, Manheimer and Glanville, 2011) namely

MEDLINE, CINAHL, EMBASE, Allied and Complementary Medicine Database (AMED), Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, Scopus, OT Seeker, PEDro, ETHOS and Web of Science (science and social science citation index) and OpenGrey. Hand searching the reference lists of key studies for additional trials was also undertaken (Dickersin, Scherer and Lefebvre, 1994). No language or date restrictions were applied, and the search was conducted on the 17 October 2018. The review was updated on 22.04.2020; while there were an additional 1,089 hits, no new papers - meeting the inclusion criteria - were identified.

The search terms integrated into the systematic search were developed from the review question using the PICOS components (Bettany-Saltikov, 2010; Lefebvre, Manheimer and Glanville, 2011). Terms from the PICOS model were identified, and then, synonyms for the population and intervention components were identified (Table 1). Examples of the specific search strategies used can be seen in Appendix A. The relevant intervention, outcome, and study components were then applied either as limiters or during the screening process of the studies identified. Search filters for RCTs were applied to the MEDLINE, CINAHL and PsycInfo searches. Other limiters applied were to include only adult human participants. The titles and abstracts of the search results were initially screened, merged, and duplicates removed using reference management software, by the first author. After an initial sift of title and abstracts (conducted by two of the authors, AG and JA), a second sift was undertaken, where each article was read in full and retained or removed depending upon the inclusion/exclusion criteria (as agreed by two of the authors, AG and JA). Any discrepancies that could not be resolved by discussion, were resolved by a third author (CR).

Methodological quality assessment

The Cochrane collaborations' tool for assessing risk of bias in RCTs (Higgins, Altman and Sterne, 2011) was independently applied to each included study by two reviewers (AG and

CR). Where there was insufficient information for appraisal of bias the original authors were contacted for further information. A domain-based evaluation of potential biases in RCTs was carried out in which seven risk of bias questions were marked for a low, high or unclear risk of bias.

Data collection process

A Data extraction template was developed by one of the authors (AG) using an adapted version of the Cochrane Collaboration's template for data collection. The data extraction forms obtained data relating to study eligibility, methodological characteristics of included studies, participant characteristics (age and gender), intervention group characteristics (number of groups, specifics of the intervention, dosage/timings), outcome characteristics (names of primary and secondary outcome measures and upper/lower limits), risk of bias assessment, data analysis (mean differences and estimates of effect with confidence intervals; p-values), and key study conclusions. Data extraction was undertaken by four of the authors (AG, NL, JA, SO), with two extractors for each study.

Data analysis and synthesis

A narrative synthesis approach was used throughout as the heterogeneity of the studies rendered meta-analysis inappropriate (Bettany-Saltikov, 2010; Deeks, Higgins and Altman, 2011). Nevertheless, to help interpret the clinical relevance of the mean treatment effect of the specific intervention in each individual study, the standardised mean difference (effect size) of each intervention (between group difference/standard deviation of the baseline values) was calculated, with effect sizes of 0.2, 0.5, and 0.8 considered to be small, medium and large, respectively (Cohen, 1988). In addition, the between-groups mean differences and p-values that were reported in each study were presented where possible. A clinically

important between-groups mean difference was defined as 10% (1-point decrease on a 0-10 scale for pain severity) (NICE, 2016). The GRADE approach, as specified in the Cochrane Handbook (Schunemann et al., 2011) was used by three authors (AG, CR and AM) to assess the certainty (or quality) of evidence based on the consideration of four domains: risk of bias, inconsistency, indirectness and imprecision. This allowed for an overall judgement to be made across the studies.

RESULTS

The electronic search yielded 11,444 records and hand searching yielded an additional one record. Duplicates were removed leaving 5,486 records, of which study titles and abstracts were screened against the set eligibility criteria. 32 full texts were accessed. Of these, 12 studies were excluded due to the studies not being RCTs, nine studies did not meet the operational definition for SDT, and one was a multi-modal intervention study (see Table 2 for excluded studies). Ten studies were included in the final review (Table 3 and Figure 1).

Characteristics of included studies

A total of 350 adult participants with CMP were included in the review with the number of participants per study ranging from eight to 75. The gender ratio was reported in eight of the ten studies, of which one study (Paolucci et al., 2016) included only female participants. The mean age of participants ranged from 39 to 65 years. Seven studies investigated SDT for patients with CLBP (Barker, Elliott, Sackley and Fairbank, 2008; Morone et al., 2012; Paolucci et al., 2012; Ryan, Harland, Drew and Martin, 2014; Trapp et al., 2015; van Baal, Schwarz, Ehrenbrusthoff and Gruneberg, 2018; Vetrano et al., 2013), two investigated SDT for people with chronic PLP (Flor, Denke, Schaefer and Grusser, 2001; Wakolbinger et al., 2018) and one study looked at SDT for women with Fibromyalgia (Paolucci et al., 2016).

Nine studies were conducted in Physiotherapy outpatient departments with one study (Flor, Denke, Schaefer and Grusser, 2001) being laboratory based. Studies were conducted in the UK, Germany, Italy and Austria. The stimulus used as part of the intervention varied; electrical pulse stimulation (n = 2), perceptive surfaces equipment (n = 4) and manual/tactile stimulation methods (n = 4). The duration of individual SDT sessions ranged from 15 to 90 minutes, with a range of three to 14 sessions, with treatment periods from 2 to 4 weeks in duration.

All ten studies assessed pain intensity, with the VAS being the most commonly used tool (five out of 10 studies). Secondary outcome measures assessed included physical function/disease-CMP-specific measures, emotional/psychological functioning, sensorimotor function, and quality of life (QoL) (see Table 5). All studies recorded a measure at baseline and immediately post treatment. The follow-up outcome measurement period ranged from two weeks (short term) (Wakolbinger et al., 2018) to six months (moderate term) (Morone et al., 2012) post treatment. There were no included studies with long-term outcome measures (>1 year).

Adverse effects reporting

Only two of the studies formally planned to assess, and explicitly asked their participants about, AEs (Barker, Elliott, Sackley and Fairbank, 2008; van Baal, Schwarz, Ehrenbrusthoff and Gruneberg, 2018). The study on SDT for patients with Fibromyalgia (Paolucci et al., 2016) reported that no patients discontinued the rehabilitation due to acute exacerbation of pain. In one study (Morone et al., 2012), five participants dropped out of the intervention group, compared to zero from the control group, with three stating a lack of time and two not providing a reason. In one study (Vetrano et al., 2013) no dropouts were recorded but the participants were encouraged to report unpleasant sensations at particular sites so they could be removed at subsequent sessions.

Deviations from the original protocol

Meta-analysis was not carried out as the interventions were delivered in such a diverse manner to different study populations that combining the results for the different studies was inappropriate. We considered meta-analysing standardised effect sizes but found that not only the treatment effects but the sample variability (indicated by the between-subjects SD) varied between studies considerably. In addition, the poor quality of the studies and low number of studies were additional factors for not undertaking a meta-analysis (Moher et al., 1998).

Methodological quality summary

The methodology across the studies was evaluated for risk of bias. This is presented as the proportion of studies with a judgement of high or low risk of bias and a summary of judgements for each of the 10 studies (Figure 2 and Figure 3, produced by using RevMan software [Review Manager. Version 5.3. Copenhagen: The Nordic Cochrane Centre. The Cochrane Collaboration, 2014]). Based on this, the methodological quality of the 10 included trials could be interpreted as low quality.

A key methodological issue in all of the included studies was the lack of blinding of participants and personnel. For example, in Flor, Denke, Shaefer, and Grusser (2001) the participants and personnel delivering the intervention were not blind to the intervention which involved electrodes being attached to the participants residual limb, which was obviously different to the standard care treatment received by the control group. Thus, the differences between groups may have been attributable to non-specific intervention effects such as the placebo effect. The lack of participant and personnel blinding illustrates the methodological challenges of blinding physical interventions such as SDT. Similarly, only two studies had adequate blinding of assessors, this is because they adequately blinded participants and the outcome measurement was self-report based. Where participants are not blind and the outcome measure is self-reported, it is impossible to have blinded outcome

assessment. Attrition bias could not be ruled out in half of the included studies. For example, in Morone et al., (2011) five (20%) participants in the intervention group dropped out compared to none in the control group. This imbalanced drop-out rate may have masked issues with the intervention. Finally, seven studies did not publish/register a protocol prior to the study thus selective reporting could not be ruled out.

The outcome of the overall quality of evidence evaluation (undertaken in accord with the Cochrane Grading of Recommendations Assessment, Development and Evaluation [GRADE] approach) is presented in Table 6.

Narrative synthesis of included studies

The pain outcomes from the ten studies are discussed in the following paragraphs and found in Table 4, and the non-pain (secondary outcome) measures are presented in Table 5.

Chronic Low Back Pain

Seven studies (Barker, Elliott, Sackley and Fairbank, 2008; Morone et al., 2011; Paolucci et al., 2012; Ryan, Harland, Drew and Martin, 2014; Trapp et al., 2015; van Baal, Schwarz, Ehrenbrusthoff and Gruneberg, 2018; Vetrano et al., 2013), assessed the efficacy of SDT in people with CLBP.

Three of these studies (Morone et al., 2011, Paolucci et al., 2012, Vetrano et al., 2013) used the Surface for Perceptive Rehabilitation [Su-Per] treatment (intervention group) which comprises deformable cones with a small top that are fixed to a rigid surface. Patients lie supine on these cones and positional changes and active exercises are performed in response to therapist guidance, resulting in many intensive perceptive stimuli. In a three arm RCT, Morone et al. (2011) showed a large effect size in favour of SDT compared to a control group, with a back-school education group also demonstrating a large effect size over the control group (Table 4). There was no difference between SDT and back school education. In

contrast, Paolucci et al. (2012) found no difference between an SDT group and a control group. Vetrano et al. (2013) compared two forms of this model (Su-Per) of SDT - the difference being whether the participants received higher tactile-pressure stimulus at the interspinous midline or not. There was a small effect size in favour of the SDT group that did not have to concentrate on the direct stimulation of the body midline, suggesting superiority of this form of Su-Per SDT.

Barker, Elliott, Sackley, and Fairbank (2008) applied SDT, via stimulation in the form of 16 vibrators closely arranged to one another on the lumbar spine and compared this to Transcutaneous Electrical Nerve Stimulation (TENS). There was no difference between groups (Table 4). This study was severely limited by malfunctioning of the SDT devices used. Ryan, Harland, Drew, and Martin (2014) delivered tactile acuity training and graphesthesia training using corks and pen tops compared to a sham (control) arm. The study showed a trend to greater reduction in pain intensity for the sham control compared to the intervention group, however this pilot study raised significant questions about the fidelity of the intervention delivery. Trapp et al. (2015) compared tactile acuity training using a plastic calliper ruler to usual standard physiotherapy care. Van Baal, Schwarz, Ehrenbrusthoff, and Gruneberg (2018) also used a manual touch approach using both tactile acuity and graphesthesia techniques, compared to standard physiotherapy care. Both studies showed no statistical difference between SDT and standard care.

In summary, there was conflicting evidence from seven RCTs, conducted with people with CLBP, for the clinical efficacy of SDT compared to a control or sham treatment group on pain intensity in the immediate to medium term. The quality of the evidence was downgraded to very low quality due to very serious limitations with risk of bias and serious limitations with inconsistency, imprecision and indirectness (Table 6).

Phantom Limb Pain

Two studies investigated the efficacy of SDT for PLP in comparison with standard care that comprised a comprehensive psychophysiological assessment (Flor, Denke, Schaefer and Grusser, 2001) or residual limb massage (Wakolbinger et al., 2018). Both studies used the West-Haven Yale Multi-Purpose Inventory (WHYMPI) to record pain intensity (0-6, 0 = no pain, 6 = very intense pain) and both demonstrated a large effect size in favour of the SDT group (Table 4). However, the sample size in both studies were very low ($n \leq 10$).

In summary, there was very low-quality evidence from two studies supporting the efficacy of SDT for phantom limb pain (PLP) compared to a control/sham treatment, on pain intensity in the immediate to medium term. The quality of the evidence was downgraded due to a very serious limitation in terms of risk of bias and serious limitations with inconsistency, imprecision and indirectness (Table 6).

Fibromyalgia

One study investigated the efficacy of SDT on Fibromyalgia, in comparison with an exercise group and a control group who received one brief educational session (Paolucci et al., 2016). Pain intensity was measured via the Self-Assessment Pain Scale (SAPS) on a 0-10 scale. A medium effect size in favour of the SDT groups was shown compared to the control group (Table 4). There was no difference between the SDT and the exercise group.

In summary, there was very low-quality evidence from one study supporting the efficacy of SDT for pain in people with Fibromyalgia compared to a control group. The quality of the evidence was downgraded due to serious limitations with risk of bias, inconsistency, imprecision and indirectness (Table 6).

Secondary Outcome Measures

There were several outcome measures reported that, under our protocol, were classified as secondary outcome measures, including physical function/disease specific measures, emotional functioning, sensorimotor function and Quality-of-Life (QoL) (Table 5). The outcome measures used throughout these domains were disparate, hence, no clear narrative could be made on SDT versus a control/comparator, thus no evidence statements regarding these secondary outcome measures have been made. The only secondary outcome measure that showed commonality was Two-Point Discrimination (TPD) testing, within the sensorimotor function domain. Van Baal, Schwarz, Ehrenbrusthoff, and Gruneberg 2018 and Trapp et al, 2015 demonstrated large effect sizes in favour of SDT, indicating an improvement in tactile acuity post SDT intervention (Table 5). None of the 10 studies measured Quality-of-Life (QoL) as an outcome measure.

DISCUSSION

This systematic review aimed to investigate the efficacy of SDT for people with CMP. Ten RCTs were included in the final review including 350 participants incorporating three distinct CMP conditions; CLBP (seven studies), PLP (two studies) and Fibromyalgia (one study). This is the first comprehensive review of SDT to include CMP rather than just CLBP. This review can be viewed as updating and building upon the two existing systematic reviews of SDT for people with CLBP (Daffada et al. 2015; Kalin et al. 2016) by including a further five RCT studies; two focussed on PLP (Flor, 2001 and Wakolbinger, 2018), one on Fibromyalgia (Paolucci et al., 2016) and two further studies with CLBP patients (Trapp et al., 2015 and Van Baal Schwarz, Ehrenbrusthoff, and Gruneberg, 2018). This study, therefore, fills an important gap in the literature and provides much needed, up-to-date guidance for clinicians on the current state of the evidence with regard to efficacy and safety. The high risk of bias of

the studies in the review reduces the capacity to make any firm recommendations about the efficacy of SDT, although from the limited available evidence the intervention demonstrates promise, particularly for people living with PLP. Given the paucity of RCTs, investigating the efficacy of SDT in CMP, it is appropriate to briefly explore the non-RCT evidence identified within our search (Table 7). Thirteen non-RCTs were identified, five in people with CRPS, four in people with CLBP, three in people with PLP and one in people with knee osteoarthritis (OA). Eleven out of the 13 studies were of a single case/single group design where SDT was combined with other interventions (Table 7). Of note, are two well controlled, within-subject repeated design studies in people with CRPS, which both reported statistically and clinically meaningful improvements in pain, when SDT was compared to a well-matched control (Moseley et al. 2008; Moseley and Wiech, 2009). The majority of these studies (see Table 7) demonstrated clinically worthwhile improvements; however, given the design, no claims of cause and effect can be attributed to SDT. Thus, in keeping with our registered protocol, these non-RCTs were not used to inform our clinical recommendations. In nine of the 10 included RCT studies SDT was delivered by a healthcare professional or caregiver while in the study by Barker et al. (2008) an automated SDT device was employed, facilitating self-application. In seven of the studies (Flor, Denke, Schaefer, and Grusser, 2001; Morone et al., 2001; Paolucci et al., 2012, Paolucci et al., 2016; Trapp et al., 2015; van Baal, Schwarz, Ehenrenbrusthoff, and Gruneberg, 2018, and Wakolbinger et al., 2017) individuals within the intervention group, whilst receiving SDT, indirectly received more contact time with a therapist than individuals in the control group. Paolucci et al. (2016) argued that the one-to one-relationship between the therapist and participant in the SDT group may have contributed to the positive findings in comparison to the control group. Paolucci et al. (2016) argued that the one-to one-relationship between the therapist and

participant in the SDT group may have contributed to the positive findings in comparison to the control group.

With regard to the safety of SDT, none of the included studies reported any AEs. The analysis of studies that were excluded from our review (see Table 2), showed that only three (Schmid et al., 2017; Walti, Kool, and Luomajaki, 2015; Wand et al., 2013) made any reference to safety issues or AEs. Specifically, Wand et al., (2013) discussed that the application of a stimulus using a penetrating needle should be avoided, and a plausible, safer and equally effective treatment could be discrimination training using non-penetrative stimulation but did not report any AEs. Schmid et al., (2017) and Wälti, Kool and Luomajoki (2015) also reported no AEs for a two-week home-based sensory-motor self-training intervention with people with CRPS and a sensory retraining tool which used a home training interface via the web, respectively. In summary, our review found that SDT, as delivered within the parameters of this review, would appear to be safe.

Strengths and limitations

A strength of this review is its adherence to the Cochrane Collaboration methodology (Higgins and Green, 2011). Attempts were made to contact all authors in which the published study did not provide sufficient explanation to make a judgement in accordance with the GRADE risk of bias questions. This was necessary for seven of the ten studies with all authors replying, and the risk of bias judgements (Figure 2 and Figure 3) were updated accordingly. However, it should be noted that the GRADE process could not be fully applied here, as meta-analysis was not warranted given the heterogeneity of the population and the application of the intervention. Furthermore, there were too few studies to enable subgrouping into differing CMP conditions as part of the data pooling meta-analysis process. The lack of an agreed upon definition for SDT in the literature also made the systematic

reviewing process difficult, in terms of a wide search strategy that produced imprecise results. Overall, the primary limitation of this review was the quality of individual studies included, all of which were small studies with a high risk of bias.

Clinical implications

Given the high risk of bias within the included studies no firm clinical recommendations can be made. GRADE rated recommendations show all studies to be of very low certainty (or quality) of evidence, with the rationale shown in Table 6. Given that the studies included were small and largely underpowered, the standardised mean effect sizes have been calculated for each study to explore the potential magnitude of the effect for this intervention. The effect sizes ranged from medium in the direction of the control group to large in favour of SDT. We have also identified which studies reported a statistically significant finding and a between groups difference above the MCID. However, we have not attempted to interpret the data any further to avoid simply counting the number of studies demonstrating a statistically significant effect or a large effect size, which can lead to erroneous conclusions. The absence of any reporting of AEs has important clinical implications, as it suggests SDT could potentially be more appealing than other interventions in certain circumstances, for example in the treatment of people with PLP where pharmacological treatments have shown limited efficacy and are associated with high levels of AEs (Alviar, Hale and Lim-Dungca, 2016).

Future research

This review highlights the lack of high quality published RCT's on SDT for people with CMP and the need for adequately powered high quality RCTs to be carried out addressing the existing key study limitations around issues such as blinding and controlling for patient-therapist contact time. In addition, SDT is delivered within the existing literature in a

heterogeneous manner, future work should investigate which modes of SDT are most effective (e.g. electrical stimulation vs. tactile stimulation) along with key delivery parameters such as optimising dosage.

CONCLUSION

In this systematic review, ten RCTs (consisting of 350 participants) of very low quality were identified that have investigated the efficacy of SDT for people with CMP. There was conflicting evidence from seven RCTs for the efficacy of SDT for CLBP. There was very low-quality evidence from two studies supporting the efficacy of SDT for PLP. There was very low-quality evidence from one RCT for the efficacy of SDT for Fibromyalgia. No AEs of SDT were identified. However, the high risk of bias within the existing literature means that no firm conclusions can be made at this time. Overall, there is a lack of high-quality evidence investigating the efficacy and safety of SDT to guide its use in the clinical management of CMP.

Declaration of interest

Two of the authors (CR and DM) are named inventors on a patent under submission for a novel sensory discrimination training based medical device that could potentially be used for the treatment of chronic pain. The lead author's PhD studies received part funding from Medi-Direct Ltd., a company with financial interest in the aforementioned sensory discrimination based medical device. The remaining authors have no conflicts of interest to declare.

Figure 1: Flow (PRISMA) diagram of the study selection process

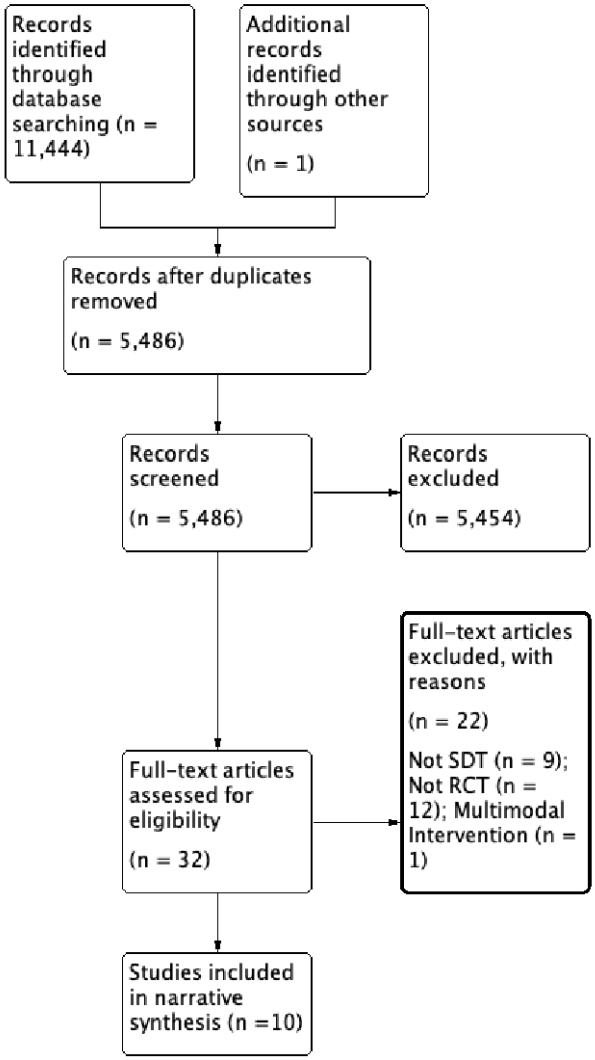

Figure 2: Risk of Bias Graph

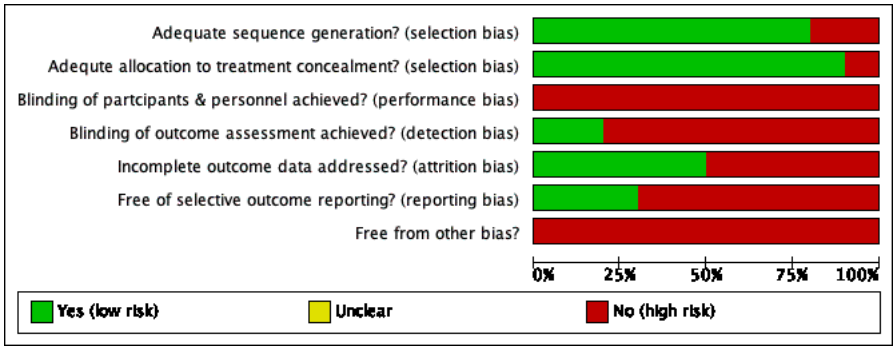

Figure 3: Risk of Bias Summary

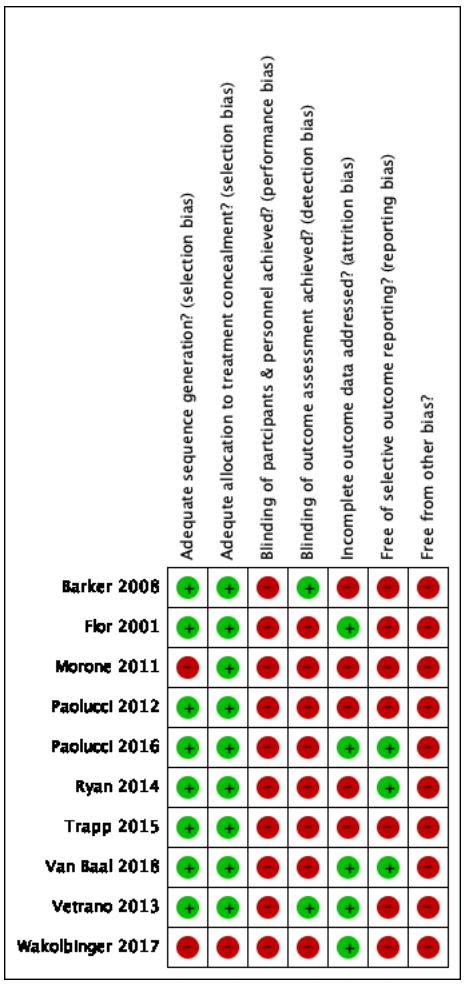

Table 1. Review questions PICOS model and search terms.

PICOS	Population	Intervention	Outcome	Study Design
Definition	Adults with chronic musculoskeletal pain.	Sensory discrimination training.	Pain, health and wellbeing.	Randomized Controlled Trials.
Subject headings (MeSH headings)	Chronic pain, musculoskeletal pain, osteoarthritis, rheumatoid arthritis, Fibromyalgia, myalgia.	Discrimination Learning, pain threshold, pain perception, sensory feedback.	Pain intensity, physical function, sensorimotor function, patient satisfaction, health related quality of life, disease specific measures, adverse events.	
Text words	Persistent pain.	Sensory discrimination training, sensory re-education, sensory training, discrimination training, sensorimotor training, Sensorimotor discrimination, tactile acuity, perceptive rehabilitation.		Randomized controlled trial, randomized, placebo, drug therapy, randomly, trial, groups

Table 2. Excluded Studies

Number	Reference	Reason Excluded
1	Albornoz-Cabello et al, 2017	Intervention not SDT
2	Gomiero et al., 2018	Intervention not SDT
3	Gutknecht et al., 2015	Intervention not SDT
4	Hargrove et al., 2012	Intervention not SDT
5	Harms et al., 2020	Method not RCT
6	Hohmann et al., 2012	Intervention not SDT
7	Jin Ah et al., 2013	Intervention not SDT
8	Kerem & Yigiter, 2002	Intervention not SDT
9	Koller & Baumgartner, 2017	Method not RCT
10	Koller & Luomajoki, 2013	Method not RCT
11	Letafaker et al., 2017	Intervention not SDT
12	Louw et al., 2015	Method not RCT
13	McCabe, Harris & Grieve 2011	Method not RCT
14	McCaskey et al., 2018	Intervention not SDT
15	Moseley, Zalucki & Wiech 2008	Method not RCT
16	Moseley & Wiech, 2009	Method not RCT
17	Nishigami et al., 2015	Method not RCT
18	Osumi et al., 2012	Method not RCT
19	Schmid et al., 2017	Method not RCT
20	Schneider et al., 2015	Method not RCT
21	Walti, Kool & Luomajki, 2015	Multimodal intervention so SDT comparison not possible
22	Wand et al., 2013	Method not RCT

Table 3: Summary of Included RCT Studies

Study (setting)	Participants	Interventions and comparator/control	Outcomes	Comments
Barker et al., 2008 Setting: Physiotherapy Department at the Nuffield Orthopaedic Centre NHS, Oxford, UK. Informed consent: Yes; Ethics approval: Yes	CLBP >3 months duration. *n* = 60 (30 intervention; 30 control); 30 males Mean age (years): 53.4	FairMed Stimulation: hand-held controller with subject interface and an array of 16 vibrating stimulation points applied around the lumbar spine. User indication on controller interface which point they judge has been stimulated. Device response correct or incorrect. 30-minute sessions over 3 weeks; approximate Total duration time based on use once per day for 15 days = 450 minutes. TENS control group – portable TENS TPN 200PLUS unit, (parameters of 80 and 100 Hz). Two surface electrodes at distance of 5cm – 20 cm to painful area. Use as often as required; intensity adjusted to produce tingling sensation, approx. 2-3 times sensory threshold.	Pain: VAS (0 – 100mm). ODI (0 – 100); PSE (0-60); TSK (17-60); PCS (0-52); HADS-A; HADS-D; Sit to stand (n/min), stair climb (n/min) & walk distance (metres/5 min). Baseline; 3, 6 & 12week follow-up.	Significant technical errors reported with Fairmed; 20/32 participants reported fault during intervention phase.
Flor et al., 2001 Setting: Laboratory, Germany Informed consent: Yes; Ethics Approval: Yes	PLP (all upper limb amputees) *n* = 10 (5 intervention; 5 control); 8 males Mean age (years): 55.4	SDT: 8 electrodes attached to skin of stump. 80 trials of frequency/80 of location training per session. Difficulty increased > 60% correct responses per ten-trial block. 10 x 90 mins per day over 2 weeks; Total duration time = 900 minutes. Standard Care: Analgesic Medication, Nerve stimulation, or Physiotherapy; Total duration time = 720 minutes	WHY- MPI (0-6) TPDT (location and frequency of stimulus); fMRI of cortical (re)organisation. Baseline; 2 weeks & 3 months follow-up.	
Morone et al; 2011 Setting: outpatient department, Rome, Italy	CLBP > 3 months duration. *n overall* = 75 Intervention group: *n = 25*; 21 females Mean age (years): 52.7 Comparison group: *n* = 25; 16 females	Intervention group: Surface for perceptive rehabilitation (Su-Per treatment): deformable cones with small top fixed to rigid surface. Patients lay on cones - weight supported by reaction force vectors. High pressure to small area = intensive stimuli. Training involved performing perceptive tasks to rehabilitate perception of trunk and midline. Provided by physical therapist at a clinic. 45 mins, 3 times per week for roughly one month; approximate total duration time = 540 minutes.	VAS (0-100mm); MPQ PRI (0-78); ODI (0 – 100); WDI (0 – 9) Baseline; 4, 12 & 24 weeks.	
Informed consent: Yes; Ethics Approval: Yes	Mean age (years): 55.4 Control group: *n = 25,* 17 females Mean age (years): 57.8	Comparison group (Back-School): one theory session and three practical sessions on re-education of breathing, self-stretching of the trunk muscles, erector spine reinforcement, abdominal reinforcement and postural exercises. Attended in subgroups of 4-5 patients over 4 weeks. Control group: medical and pharmacological assistance only (same regimen as in intervention and comparison groups for same period).		
Paolucci et al., 2012 Setting: outpatient department, Rome, Italy; Informed consent: Yes; Ethics Approval: Yes	CLBP > 3 months duration. *n* = 30 (15 intervention; 15 control); male to female ratio not reported Mean age (years): 58.7	Su-Per treatment as per Morone et.al, 2011 study Duration of intervention: 3 sessions (45 minutes) per week over 1 month; Approximate total duration time = 540 minutes. Control group (Back school) followed the same protocol in Morone et. al, 2011 Duration of control group: 3 sessions (45 minutes) per week over 1 month (i.e. same treatment duration as intervention group).	MPQ (Global Score - PRI 0 – 100) Baseline and at end of treatment (one month)	Stabilometric assessment i.e. centre of pressure of body was primary outcome measurement but not relevant to this review.
Paolucci et. al, 2016 Setting: Physical medicine and rehabilitation unit, Rome (Italy). Informed consent: Yes Ethics: Yes, (Committee Number 2547-720/2012; Clinical Trial Number 02472093)	Fibromyalgia diagnosis *n overall* = 62 Intervention (PS) group: *n* = 20; all female Mean age (years): 49.3 Comparison (PE) group: *n* = 21; all female Mean age (years): 49.3 Control group (CG): *n* = 21; all female Mean age (years): 51.3	Su-Per treatment as per Morone et.al, 2011 protocol. Duration of intervention: 10 sessions, twice a week; Total duration time = 540 minutes Comparison (PE) group = Attended in subgroups of 4. Brief educational session. Physio led aerobic training, posture exercises for trunk in supine position to improve axial stability, inc. diaphragmatic breathing. Ten 1-hour sessions, twice a week (over 5-week period); total duration time = 600 minutes Control group: 1 brief educational session - simple breathing exercises/relaxation techniques and stretching exercises. 1 hr taught + at least 2 hours per week for 5-week period; total duration time approx. 600 minutes.	Fibromyalgia assessment status - SAPS; FIQ; HAQ Baseline; 5 weeks & 12-week follow-up.	Authors acknowledged importance of therapeutic alliance on treatment effects as PS and PE groups (both groups with success) were supervised/guided from a physical therapist and the control group was not.

Ryan et.al, 2014 Setting: NHS Physiotherapy outpatient department, UK Informed consent: Yes Ethical approval: Yes ISRCTN 98118082	CLBP > 6 months *n =24* Intervention group: *n* = 12, Gender ratio not stated Mean age (years): 45 Control group: *n* = 12 Gender ratio not stated Mean age (years): 46	Intervention: (1) Tactile acuity training - five/ten sites of painful area marked based on TPDT. Sites stimulated in random order using a big (wine bottle cork) or small (pen top) probe. 3 blocks of 24 stimuli randomly applied over approx. 24 minutes. >90% of the answers correct = difficulty increased as marks moved 10% closer. Repeated for home training program. (2) Graphesthesia acuity training – 60 letters (about 1 inch high) traced on painful area by clinician or carer. Guided feedback on letter dentification if incorrect. Control group: sham tactile stimulation – participants received same tactile stimulation as intervention group, but they did not focus on stimulus and therefore had no interaction with the carer. Total duration time: 12 sessions; 3 sessions (intervention or placebo) provided by the physiotherapist and the rest were delivered by an informal carer.	VAS (0 -100mm); RMDQ (0 – 24) Baseline, pre and post treatment.	In the sham tactile stimulation (control) group, 6 participants were lost (for several reasons), which is half of this group's test size.
Trapp et. al, 2015 Setting: Outpatient orthopaedic rehabilitation unit Informed consent: Yes; Ethical approval: Yes	CLBP >3 months duration. *n* = 30 Intervention group: n = 15; 10 males Mean age (years): 45.5 Control group: n = 15; 9 males Mean age (years): 40.6	Intervention group: 'Visual Feedback'- (1) TPDT taken; (2) Lumbar musculus multifidus exercises practiced for about 10 minutes whilst watching video footage of this movement; (3) Stimulation received, visual feedback from webcam on whether their judgement was correct. Procedure repeated 10 times for each side. 3 sessions per week approx. 20 minutes each, over 2 weeks; total duration time = 120 minutes. Control group: 30-minute sessions - physiotherapy, relaxation training and movement training (walking); total duration time = 180 minutes.	VAS pain (0 -10); TPDT (cm); BDI Depression, HAMD depression; MPI section I, II and III (0-7). PASS total, PCS total, PVAQ total. Baseline and 14 days.	
Van Baal et. al, 2018 Setting: Physiotherapy department Informed consent: Yes Ethical approval: Yes; DRKS00007116	CLBP > 3 months Overall *n* = 9 Intervention Group *n* = 4 Gender ratio not stated. Mean age (years): 56 Control Group *n* = 5 Gender ratio not stated. Mean age (years): 50	Intervention: Graphesthesia training - (1) letters (25cm squared for letter size) were drawn once on lower back and participant told which letter was being drawn (2) Three sets of 20 letters (60 total) drawn on predefined area of back using Knitting needle (3mm prong). Participants were asked to name a letter, even if they were unsure of which letter had been drawn. Incorrect responses corrected by therapist and re-drawn to facilitate learning. x2 20-minute sessions before or after normal care physio sessions for 3 weeks; Total duration time = 120 minutes + usual care. Control group: Physiotherapy usual care (did not include sensory training approaches similar to graphesthesia training).	SF-36; RMDQ; BPI; TPDT; Qualitative feasibility of the intervention. Baseline & 3 weeks.	Translation from German to English provided by one of the papers authors.
Vetrano et. al, 2013 Setting: outpatient academic hospital in Rome, Italy. Informed consent: Yes. Ethical approval: Yes, local ethics committee.	CLBP > 3 months duration Overall *n* = 40. Intervention group: n = 20; Gender ratio not stated Mean age (years): 52.6 Control group: n = 20; gender ratio not stated Mean age (years): 52.2	Intervention: Su-Per Treatment - same protocol as Morone et. al, 2011 x3 sessions per week of 30-40 mins for 1 month; total duration time = 480 minutes. Comparator: Modified Su-Per Treatment same as the standard SU-PER treatment but used more deformable cones and without patient's attention fixated upon the body midline.	Primary: VAS pain (0 – 100mm); MPQ, ODI (0-100). Baseline, end of treatment, 4 and 12 weeks after.	Comparison study between two forms of SDT
Wakolbinger et. al, 2017 Setting: Outpatient department,	PLP (upper and lower limb amputees) Overall *n* = 8 Intervention group: *n* = 3; 2 males Mean age (years): 39 Control group: *n* = 3; 3 males Mean age (years): 46 Non-randomized group *n* = 2; 2 males Mean age (years): 65	Intervention group: Tactile Discrimination Training (TDT) - cotton swabs used to stimulate the skin on residual limb. Two blocks of 50 stimuli; four points were stimulated in a pseudo-randomized order; verbal report the number of stimulated point, correct or incorrect response noted and difficulty increased based on >70% correct response resulting in 2mm reduction in distance between points. 15 mins per day for two weeks; total duration time = 210 minutes. The control group received 15 minutes of daily residual limb massage for two weeks (by a family member, initially instructed by a physiotherapist).	WHY-MPI (0-100mm); change in phantom length/telescoping (% change) Baseline, end of treatment, two weeks and four weeks after.	

Table 4. Pain outcomes reported in the RCTS.

Condition; study	Mean (CI) between groups difference	Standardized Mean Difference - Effect Size (Cohen's-d*)	Statistical significance (p-value)	Clinical relevance (MCID**)
CLBP; Barker 2008	0.1 (-0.37 to 0.57) favours SDT	0.06 - small	No, p = 0.83	No
CLBP; Ryan 2014	2.47 (-0.7 to 51.9) favours control	1.00 - large	No, p = 0.056	No, favoured control
CLBP; Morone 2011	3.00 (1.89 to 4.11) favours SDT over control group	2.70 = large	Yes, p <0.001	Yes
CLBP; Paolucci 2012	2.00 (-0.59 to 4.59) favours SDT over back education (control group)	0.09 = small	No, p = 0.436	No
CLBP; Trapp 2015	1.32 (-6.61 to 9.25) favours SDT	0.71 - medium	No, p = 0.866	Yes
CLBP; van Baal 2018	0.02 (-0.06 to 0.10) favours SDT	0.01 - small	No, p = 0.56	No
CLBP; Vetrano 2014	0.5 (0.13 to 0.87) favours SDT over SDT (midline)	0.26 = small	No, p = 0.179	No
Fibromyalgia; Paolucci 2016	0.9 (0.50 to 1.30) favours SDT	0.75 (SDT) = medium	Yes, p = 0.003	No
PLP; Flor 2001	1.95 (1.32 to 2.58) favours SDT	1.14 = large	Yes, p = 0.008	Yes
PLP; Wakolbinger 2018	1.5 (0.97 to 2.03) favours SDT	0.90 = large	Yes, p = 0.0215	Yes

BPI = Brief Pain Inventory (0-10); CI = 95% confidence intervals (in parenthesis); FAS-SAPS = Fibromyalgia Assessment Status (0-10), Self-Assessment Pain Scale; PRI = Pain rating Index (0-100); VAS = Visual Analogue Scale (0-10); WHYMPI = West Haven-Yale Multidimensional Pain Inventory (0-6). * Cohen's d: small 0.20, medium 0.50, large 0.80. **MCID: >10% decrease.

Table 5. Secondary Outcome Measures.

Condition; Study	Physical/Disease Specific Function	Psychological/Emotional functioning	Sensorimotor function	Quality of Life	Adverse events
CLBP, Barker 2008	ODI: favours sham; mean diff 0.3 (-0.43 - 0.63), SMD = 0.02 [p =0.85] Sit to Stand: Same effect mean diff 0, [p= 0.90] Stairs favours SDT; mean diff 0.1 (-0.31 to 0.51), SMD = 0.04 [p = 0.81] Walk distance: favours SDT; mean diff 6.0 (-4.79 to 16.79), SMD = 0.06 [p = 0.58]	PSE: favours sham; mean diff 2.5 (0.53 to 4.47), SMD = 0.23 [p = 0.21] PCS: favours sham; mean diff 0.4 (-1.57 to 2.37), SMD = 0.03 [p= 0.84] TSK: favours sham; mean diff 0.2 (-2.45 to 2.85), SMD = 0.03 [p=0.94] HAD-A: favours SDT; mean diff 1.1 (0.35 to 1.85), Baseline SD not reported, [p= 0.14) HAD-D: favours sham; mean diff 0.4 (-0.18 to 0.98), Baseline SD not reported [p=0.49])	Not measured	Not measured	Nil reported (Technical errors reported with 20 of the 32 Fairmed (SDT) device during trial)
CLBP; Ryan 2014	RMDQ: favours control; mean diff 2.2 (1.6 to 6), SMD = 0.33, p= 0.237)	Not measured	Not measured	Not measured	Nil reported
CLBP; Trapp 2015	Not measured	BDI: favours SDT; mean diff 0.86 (-2.22 to 3.94), SMD = 0.13 [p =0.777] HAMD: favours SDT; mean diff 0.60 (-5.86 to 7.06), SMD = 0.31 [p= 0.925]	TPDT (mm) favours SDT; mean diff 16.6 (5.3 to 27.9), SMD = 1.27 [p= 0.144]	Not measured	Nil reported
		PASS total: favours SDT; mean diff 10.33 (-0.15 - 20.81), SMD = 0.31, [p=0.322] PCS total: favours SDT; mean diff 2.03 (-6.2 to 10.27), SMD = 0.17, [p=0.803] PVAQ total: favours SDT; mean diff 6.86 (0.42 to 13.26), SMD = 0.52 [p=0.812]			
CLBP; van Baal 2018	RMDQ: favours SDT mean diff 0.9 (-0.06 - 0.10), SMD = 0.17 [p=0.17]	SF-36 mental well-being: favours SDT mean diff 10 (4.89 to 15.11), SMD = 0.49, [p = 0.06] SF-36 emotional functioning: favours SDT; mean diff 25 (-55.7 to 105.7), SMD = 0.51 [p = 0.73]	TPDT favours SDT; mean diff 13 (3 to 37.35), SMD = 1.11, [p = 0.56]	Not measured	Nil reported
CLBP; Morone 2011	ODI: favours SDT; mean diff 16 (9.79 to 22.2), SMD = 0.31 [p = 0.403] WDI favours SDT; mean diff 1 (0.04 to 1.96), SMD = 1.33 [p= 0.302]	Not measured	Not measured	Not measured	Nil reported
CLBP; Paolucci 2012	Not measured	Not measured	Not measured (stabliometric measurement only)	Not measured	Nil reported
CLBP; Vetrano 2013 (comparison study between two forms of SDT)	ODI - favoured SDT over SDT with midline awareness; mean diff 2 (3 to 3.92), SMD= 0.13 [p = 0.299]	Not measured	Not measured	Not measured	Nil reported

Fibromyalgia; Paolucci 2016	HAQ favours SDT Mean diff 0.1(0.06 to 0.14), SMD = 0.22 [p = 0.009] FIQ favours SDT; Mean diff 10 (6.12 to 13.88), SMD = 0.57 [p=0.013] FAS favours SDT Mean diff 0.9 (0.60 to 1.20), SMD = 0.75, [p =0.004]	Not measured	Not measured	Not measured	Nil reported
PLP; Flor 2001	Not measured	Not measured	TPDT favours SDT* (p=0.005)	Not measured	Nil reported
PLP; Wakolbinger 2018	Not measured	Not measured	Not measured	Not measured	Nil reported

Abbreviations: BDI: Beck depression inventory; FAS: Fibromyalgia assessment scale; FIQ: Fibromyalgia impact questionnaire; HAMD: Hamilton depression scale; HADS-A: Hospital anxiety and depression scale – anxiety; HADS-D: Hospital anxiety and depression scale – depression; HAMD: Hamilton depression scale; ODI: Oswestry Disability Index; PCS: Pain catastrophising scale; PASS: Pain anxiety symptom scale; PVAQ: Pain vigilance and awareness questionnaire; Pain self-efficacy; SF-36: 36 item short-form health survey; SMD: standardized mean difference; TPDT: Two-Point discrimination threshold. 95% confidence intervals (in parenthesis) *TPDT mean difference not reported.

Table 6. Summary of Findings **(GRADE)**

Overview	**Method**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Certainty of evidence (GRADE)**
CLBP n = 270 (7 studies)	RCT	Very Serious limitation ¶†‡	Serious limitation **	Serious limitation #	Serious limitation §	⊕⊖⊖⊖ Very Low
PLP n = 18 (2 studies)	RCT	Very Serious limitation ¶ †‡	Serious limitation **	Serious limitation #	Serious limitation §	⊕⊖⊖⊖ Very Low
FIBROMYALGIA n = 62 (1 study)	RCT	Serious limitation †	Serious limitation **	Serious limitation #	Serious limitation §	⊕⊖⊖⊖ Very Low

¶ Allocation and/or concealment bias (selection bias); †No blinding of outcomes and/or assessors (performance/detection bias); ‡No registered protocol (selective reporting bias); ** High heterogeneity/variability in results (inconsistency); # Heterogeneity in type/application of intervention (indirectness); §Small Sample Size (imprecision). GRADE:
Grading of Recommendations Assessment, Development and Evaluation; very low = this research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different is very high (N.B. Substantially different = a large enough difference that it might affect a decision).

Table 7. Summary of Non-Randomised studies of SDT intervention

Study Method	**Participants (condition, sample size, gender, mean age)**	**SDT Delivery Method (equipment and dosage details)**	**Summary of results**
Harms et al., 2020 Randomized replicated case series - feasibility study	Knee Osteoarthritis *n* = 10 7 females 60	Touch discrimination training (TDT): sharpened pencil tip or a rubber tip. Duration: TDT for at least 15 min twice a day (i.e., 7–8 min for each side of the knee).	No significant positive effects on pain and function. Four participants did not perform TDT sessions due to lack of willingness and/or timely availability of a person to assist. TDT application by "significant other" not feasible delivery method and represents a significant barrier to its use.
Koller & Luomajoki, 2013* Case study	PLP (arm) *n* = 1 male 43	Two-Point discrimination (TPD) training: electronic caliper. Photo of residual limb (4 points marked on the photo). Duration: 3 times per day for 5 consecutive days. Then 3 weeks of 10 mins per day.	Phantom modalities (pain, feeling and sensation) combined = reduction of 4.13/10 (VAS). TPD improvement = 0.67 cm.
Koller & Baumgartner, 2017* Case Study	PLP (below knee amputee) *n* = 1 male 28	Automated two-point discrimination (TPD) device applied to stump: electric motor devise with control unit - assisted by therapist. Duration: 10 mins per day for 19 days.	Phantom modalities (pain, feeling and sensation) = reduction of 2.3/10 (VAS). Shooting pains reduced from 3.7/10 to 2.0/10 (VAS). Evening/nightly attacks of 10/10 (VAS) no longer occurred during the intervention phase.
Louw et al., 2015 Case series	CLBP *n* = 16 12 females 48	9-block grid shown on a body chart. TPD = back of a pen. Duration: 5 minutes per block grid. Randomly selected. Progression based on correct/incorrect answers. 45 minutes total.	Mean pain ratings on NRS reduced by 1.91 (range 0-6). Mean forward flexion improved by 4.82cm (range -1 to 21).
McCabe, Harris & Grieve, 2011 Exploratory study	CRPS *n* = 14 9 females 44	Electrical sensory discrimination therapy (ESDT): 4 electrode system device. Duration: 3x 30-minute sessions per week. Control group = Physical rehabilitation and psychological support only.	Both groups = improvement on McGill Pain VAS. TPD in the intervention group only was significant (T1 = 49.9 mm - T2 = 32.6mm p = 0.03).
Moseley, Zalucki & Wiech, 2008 Within subjects repeated measures design: Four phase (A–B–C–D)	CRPS Type 1 *n* = 13 9 females 37	(A) no-treatment; (B) stimulation only (music and/or magazine during); (C) discrimination condition (see below) (D) 3-month follow-up period. Tactile stimulation sessions (in clinic): Two cork probes, photo of affected limb, random numbers table; duration: x3 6-min blocks of 24 stimuli, every weekday for 11-17 days (randomised for each participant). Home training: assistant; wine cork & pen lid; one clinic session plus one session per day at home. Discrimination phase: as above, plus interaction i.e. judgement on location of stimulus and type of probe.	2nd and 3rd phase: mean (95% CI) effect size for pain VAS = 27 mm (14–40 mm). Pain VAS not changed further at follow-up [28 mm (18–38 mm), p = 0.32], but it was still lower than it was at post-stimulation, post-waiting period or at baseline (p < 0.008 for all). Mean (95% CI) effect size for TPD was 5.7 mm (2.9–8.5 mm). TPD had not changed further at follow-up [36 mm (33–39 mm), p = 0.95], but it was still lower than it was at post-stimulation, post-waiting period or at baseline (p < 0.015 for all).
Moseley & Wiech, 2009 Within subjects repeated measures design Four phase (A–B–C–D)	CRPS of one hand or wrist *n* = 10 6 females 43	Tactile Discrimination Training (TDT): 2 probes applied to 1 of 5 stimulation sites on affected limb in random order. (A) Facing + Skin condition: watching reflected image of non-stimulated arm while facing stimulated arm. (B) Skin only condition: watching non-stimulated arm directly (C) Facing only condition: looking in direction of stimulated arm but no mirror and unaffected limb hidden (D) Control: looking away from stimulated limb with unaffected limb hidden. Duration: 3 x 6 min blocks of 24 stimuli for each condition i.e. A to D.	TPD threshold improved with training, regardless of condition (main effect of Time ($F(2, 78) = 21.73$, $p < 0.001$). Main effect of condition on TPD ($F(3, 117) = 7.49$, $p = 0.009$), driven by differences in TPD between conditions at post-session and at 2-day follow-up (Time x Condition interaction ($F(6, 234) = 11.34$, $p = 0.002$).
Nishigami et al., 2015 Case-control study	CLBP *n* = 42; 17 healthy 34 females 62	Perceived body image intervention: participants added to drawing of a back by imagining their own back in their mind and following the instructions "concentrate on where you feel your back to be…draw in the vertebra that you can feel. Do this without touching your back. Do not draw any part you cannot sense. Do not draw what you think your back looks like - draw what it feels like." Subgroups developed. TPD threshold: plastic calipers.	Perceived image of low back results: 42.8% of CNLBP patients had normal perceived body image, 28.5% expanded image, 28.5% a shrunken image. TPD distance threshold: significantly larger for expanded subgroup (13.3 ± 6.8 mm), control (5.5 ± 3.8 mm; Difference, 7.8; 95% CI, 1.83 to 13.66; p < 0.05) and normal subgroups (4.5 ± 5.5 mm; Difference, 8.8; 95%CI, 2.90 to 14.59; p < 0.05).
Osumi et al., 2012	CRPS Type 1 *n* = 1	Tactile localization training (TLT): soft square cushion - 107.9N pressure applied to left or right	Pain rating of foot in foot phase was 9.4 ± 0.54 (mean ± SD) decreasing to 4.8 ± 1.94 in the knee phase. Pain rating of the

Case Study	female 43	side of forefoot or left or right side of rear foot (TLT foot phase). The upper left, upper right, lower left, or lower right part of the patella (TLT knee phase). (1) stimulus applied (2) participant judgement on location of each tactile stimulus (3) Feedback if reported location (in)correct. Training increased from 1 to 4 sites based on success. TLT = 40 mins per day (fatigue dependent). Training on foot for 14 days, then on the knee for following 16 days.	knee in the foot phase was 7.8 ± 0.44 decreasing to 5.1 ± 1.94 in the knee phase. TPD: before TLT on knee, differences in TPD with unaffected side in the dorsum of the forefoot, the bottom of the forefoot, and the knee = 10 mm, 35 mm, and 25 mm, respectively. After TLT on knee, differences = 5 mm, 3 mm, and 10 mm, respectively.
Schmid et al., 2017 Proof of principle pilot study	CRPS Type 1 *n* = 10 7 females 58	Sensory-motor training: braille-like haptic task, different training modes (bi-manual, speed and memory training), increasing difficulty. Duration: 2 weeks training.	Pre-post VAS mean differences (1.0 ± 1.19 p = 0.023). Overall disability and depression scores showed trend to improve after 2-week training. Reduction in pain correlated with total amount of training performed.
Schneider, Koller, Meichtry & Luomajoki, 2015 ** Pilot single blind crossover study	Phantom Limb Phenomena (lower limb amputees) *n* = 8 not reported not reported	TPD training: digital photo of their stump - show area of stimulation and distinguish between 1 or 2 points of stimulation. Duration: daily10-minute training over 14 days. Control (placebo) treatment: 40-mins for 14 days	Phantom limb phenomena "painful phantom sensation" decreased by 0.29 VAS, 95% CI: 0.02–0.69).
Wand et al., 2013 Randomised, repeated measures cross-over study	CLBP *n* = 25 9 females 41	SDT: picture of back with position of each needle numbered. (1) Clinician rotated single needle following random number sequence (2) participant stated stimulating needle (3) Feedback on correct response. Duration: 20 mins - 10 mins visualisation of back, 10 mins no visualisation. Control condition: not attend to needles - therapist manipulated needles at same rate and using same random sequence as SDT condition. Duration = 20 mins.	Pain intensity (VAS) mean between group difference favours SDT (−0.8, 95% CI −1.4 to −0.3; p=0.011).
Walti, Kool & Luomajoki, 2015 RCT: SDT within Multimodal treatment (MMT)	CLBP *n* = 28 16 males 42	MMT included: (1) Pain neurophysiology education (2) Sensory retraining (3) Motor retraining. Sensory retraining: TPD threshold test - values transferred to Sensory Retraining Tool (SRT) integrated into web-based Home Treatment Interface; assistance from 1 person. Performance rated on SRT: 80% correct = treatment difficulty progressed. Duration: ≥80% completion of 55 sets	Pain reduction (NRS): between-group difference was 1.45 [0.0 to 4.0] (p = 0.03), moderate effect size of 0.66 [-0.1 to 1.5]. Disability (RMDQ): 2.02 [-1.5 to 5.6] (p = 0.25. N.B. design of the study did not allow for analysis of the sensory retraining intervention.

CLBP = Chronic low back pain; PLP = Phantom limb pain; CRPS = Complex regional pain syndrome; MDC = Minimal Detectable Change.
*German - English translation by reviewer using Translate function in Microsoft Word. **Abstract only available.

Appendix A: Search Strategy with search filter for RCTs

Medline:

Set	Query: October 04, 2018	Hits
#4	#3 AND #2 AND #1	1,082
#3	AB randomized OR AB placebo OR MW drug therapy OR AB randomly OR AB trial OR AB groups	1,514,462
#2	sensory discrimination training OR (TI (sensory discrimination (education or reeducation or training) OR (AB(sensory discrimination (education or reeducation or training)) OR TI sensory re-education OR AB sensory re-education OR TI sensory training AND AB sensory training OR TI discrimination training OR AB discrimination training OR TI sensorimotor training or sensorimotor discrimination OR AB sensorimotor training or sensorimotor discrimination OR (MH "Discrimination Learning") OR TI tactile acuity OR AB tactile acuity OR sensorimotor discrimination OR TI perceptive rehabilitation AND AB perceptive rehabilitation OR (MH "Pain Threshold") OR (MH "Pain Perception") OR (MH "Feedback, Sensory")	38,901
#1	MH pain OR MH "chronic pain" OR TI chronic n5 pain OR AB chronic n5 pain OR TI persistent pain OR AB persistent pain OR MH "musculoskeletal pain+" OR TI musculoskeletal pain OR AB musculoskeletal pain OR MH "osteoarthritis+" OR MH "Arthritis, rheumatoid+" OR MH "Fibromyalgia" OR MH "Myalgia+"	339,947

****Search updated on 21 April 2020; 81 hits.**

Web of Science:

Set	Query: 17 Oct 2018	Hits
#4	#3 AND #2 AND #1	4,215**
#3	TS= (Outcome OR effect* OR improv*)	14,469,498
#2	TS=("sensory discrimination training" OR "sensory reeducation" OR "sensory re-education" OR "sensory training" OR "discrimination training" OR "sensorimotor training" OR "sensorimotor discrimination" OR "discrimination learning" OR "tactile acuity" OR "perceptive rehabilitation" OR "pain threshold" OR "pain perception" OR "sensory feedback")	16,513
#1	TS=("Pain" OR "chronic pain" OR "persistent pain" OR "musculoskeletal pain" OR "osteoarthritis" OR "rheumatoid arthritis" OR "fibromyalgia" OR "myalgia")	734,601

**Search updated on 21 April 2020; 682 hits.

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