Title: The effect of visual feedback of body parts on pain perception: A systematic review of clinical and experimental studies

Running head: The effect of visual feedback of body parts on pain

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Significance: It was not possible to determine whether normal-sized, magnified or minified visual feedback of body parts affected pain perception in clinical or experimental settings because of contradictory findings in primary studies. This emphasises the need for higher quality studies.

ABSTRACT

Background and Objective: The aim of this systematic review was to evaluate the effect of visual feedback techniques on pain perception by analysing the effect of normal-sized, magnified or minified visual feedback of body parts on clinical and experimentally-induced pain. Databases and Data Treatment: Databases searched: Medline, Embase, PsychInfo, PEDro, CINAHL, CENTRAL and OpenSIGLE. Studies investigating pain patients and pain-free participants exposed to experimentally-induced pain were analysed separately. Risk of bias was assessed and data meta-analysed. Results: 34 studies were included. A meta-analysis of clinical data favoured mirror visual feedback (6 trials; mean difference=-13.06mm; 95%CI -23.97, -2.16). Subgroup analysis favoured mirror visual feedback when used as a course of treatment (3 trials; mean difference=-12.76mm; 95% CI -24.11, -1.40), and for complex regional pain syndrome (3 trials; standard mean difference=-1.44; 95%CI -1.88, -0.99). There is insufficient evidence to determine differences between normal-sized view and a size-distorted view of the limb. Mirror visual feedback was not superior to object view or direct view of the hand on reducing experimental pain in pain-free participants. There were inconsistencies in study findings comparing normal-sized reflection of a body part and a reflection of an object, or a magnified or minified reflection. Conclusions: There is tentative evidence that mirror visual feedback can alleviate pain when delivered as a course of treatment, and for patients with complex regional pain syndrome. It was not possible to determine whether normal-sized, magnified or minified visual feedback of body parts affects pain perception because of contradictory findings in primary studies.

Key words: Pain, Rehabilitation, Experimental Pain, Visual Feedback, Mirror Therapy

INTRODUCTION

Visual feedback (VF) of body parts has been used as a therapeutic technique to reduce pain and improve function (Thieme et al. 2012; Thieme et al. 2016). Visual feedback has been used in the rehabilitation of conditions where body parts feel large and swollen (e.g., complex regional pain syndrome (CRPS)) or small and withered (e.g., osteoarthritic hands)(Boesch et al. 2016). It is hypothesised that VF techniques facilitate re-organisation of neural circuits to their pre-pain state (Apkarian et al. 2011; Flor et al. 2006; Moseley et al. 2012; Ramachandran and Altschuler 2009; Wand et al. 2011). For example, Foell et al. (2014) investigated the use of VF for phantom limb pain (PLP) and found that the reduction in severity of PLP correlated with a reduction of dysfunctional reorganisation in the somatosensory cortex.

Visual feedback techniques include the use of mirrors, virtual reality, and real-time video capture. Generally, a normal-sized VF of a limb is used, although clinicians have attempted to improve efficacy by minifying the appearance of painfully swollen limbs and magnifying painfully withered limbs (Wittkopf and Johnson 2016). Moseley et al. (2008) studied individuals with chronic painful arms and found that magnifying the appearance of their affected arm increased movement-induced pain, and minifying the appearance of the arm reduced movement-induced pain. Experiments investigating pain-free individuals exposed to painful stimuli have been used to explore the factors influencing response to VF. Mancini et al. (2011) found that a magnified reflection of the hand reduced contact heat pain whereas a minified reflection increased pain. It is possible that mechanisms involved in visually-induced analgesia differ between patients with pain and experimentally-induced pain in pain-free participants. Cortical reorganisation has been related to pain reduction in patients with persistent pain (Diers et al. 2010; Foell et al. 2014). Reduction in activation of specific areas related to pain processing has been identified in healthy participants (Longo et al. 2012; Torta et al. 2015).

Recently, Boesch et al. (2016) reviewed the effect of producing illusions of body parts (such as VF) on pain and concluded that mirror VF reduced pain when used as a prolonged treatment. Thieme et al. (2016) reviewed the effect of movement representation techniques (including mirror VF) for treatment of limb pain and concluded that mirror VF should be considered for the treatment of patients with CRPS. These reviews did not evaluate the effect of other types of VF, such as virtual reality, and did not evaluate studies that used experimentally-induced pain to investigate early processing of nociception and analgesic mechanisms (Gracely 2006; Handwerker and Kobal 1993). The aim of this systematic review was to evaluate the effect of VF techniques on clinical pain and on

experimentally-induced pain in pain-free participants. We compared normal-sized visual feedback of body parts, using mirrors and other visual feedback techniques, against controls. We also compared normal-sized visual feedback of body parts against magnified and minified views of the body part.

METHODS

Search methods for identification of studies

This systematic review process was guided by the Cochrane Collaboration of Systematic Reviews (Higgins and Green 2011) and the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement (Moher et al. 2015). The following databases were searched from inception between 1 and 8 March 2017: Medline, Embase, PsychInfo, PEDro, CINAHL, CENTRAL, and OpenSIGLE. For the search strategy, a combination of controlled vocabulary (i.e., medical subject headings) and free-text terms were used to identify manuscripts (supporting material Appendix S1-Medline search strategy). Hand searches of the reference lists of included studies and previously published systematic reviews were conducted.

Criteria for considering studies for this review

Studies investigating participants with clinical pain or pain-free healthy subjects were included. Studies evaluating VF of any body part using mirrors, lenses, binoculars, virtual reality or video manipulations were included provided they had a control condition. Studies that did not evaluate the view of a body part on a first person perspective and/or a representation of a body part (i.e., prostheses, rubber hand, mannequins) were excluded. Studies that investigated virtual reality as a distraction and not as VF of a body part were also excluded. Studies were eligible if they were randomised controlled trials or quasi-randomised trials. Cross-over (within-subject) and parallel-group (between-subject) designs were included. Reviews, thesis, abstracts, and case studies were excluded.

Study selection

Two reviewers (PGW and MIJ) screened titles and abstracts obtained from database searches to identify potentially relevant studies, and then the full text. A third reviewer (DML) acted as arbiter. Information extracted from included studies was: study design, type of participants, patient population, sample size, type and nature of control, type and duration of visual feedback intervention, method of experimental pain induction, outcome measures, results (pain measures). Data extraction was also conducted by two independent reviewers (PGW and MIJ) with a third reviewer (DML) acting as arbiter.

Risk of bias assessment

Two reviewers independently assessed risk of bias in the studies (PGW and MIJ). It consisted of assessment of selection bias, attrition bias, blinding, and sample size. Additionally, for studies with a repeated measures design measures taken to control for cross-over effects were analysed (supporting material Table S1). For randomised controlled trials the way in which investigators dealt with drop-outs were assessed by checking the presence of intention to treat analysis. For clinical studies the Cochrane Collaboration's assessment tool was used (Higgins and Green 2011). For experimental studies the Cochrane Collaboration's assessment tool was used but adapted to account for differences in the design of the experimental studies according to their purpose. If consensus could not be reached a third reviewer (DML) acted as arbiter.

Data synthesis and analysis

The studies investigating a clinical pain condition and the studies investigating pain-free subjects were analysed separately using an identical protocol. Studies were analysed according to the use of mirrors or other VF techniques (e.g., real-time video, virtual reality, and lenses). Some studies did not use a normal-sized VF of a body part as the experimental condition but as control condition. For consistency in reporting and analysis, in these cases the control condition was classified as experimental condition. Therefore, our condition of interest was normal-sized VF of a body part.

We planned to conduct a meta-analysis if there were more than two studies using similar techniques and outcome measures (e.g., pain intensity). The number of participants and pain outcome measure mean and standard deviation post intervention was pooled and analysed using Revman 5.1 software. If it was not possible to conduct a meta-analysis, studies were individually analysed and effects sizes calculated for comparisons within each study. When further details about studies were needed the corresponding author of each study was contacted. When trials provided pain outcome results in median and range the data was transformed into mean and standard deviation following the formula proposed by Hozo et al. (2005). The mean difference (MD) and 95% confidence intervals (CI) was calculated using a random effects model in studies with parallel groups and pain intensity measured using a visual analogue scale (VAS). For pain intensity a minimally important difference of 10 mm in a 100 mm VAS was considered clinically relevant (Busse et al. 2015). Studies with multiple comparison groups were included combining the control groups creating a single pair-wise comparison (Higgins and Green 2011). Data from cross-over trials were analysed as standardised mean difference (SMD) using the generic inverse-variance random effects model. The standard error

of the SMD was calculated imputing a correlation coefficient and to allow comparisons between parallel groups and cross-over studies a correlation coefficient was imputed for both. Correlation coefficients were calculated from raw data when available, and when data were not available the correlation coefficient from a study with similar design and comparisons was used. A sensitivity analysis was conducted when a correlation coefficient was imputed, as instructed in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green 2011). When analyses resulted in a significant effect ($p \leq 0.05$) the SMD was interpreted according to Cohen's d effect size in which 0.2 = small effect, 0.5 = medium effect, and 0.8 = large effect (Cohen 1998; Higgins and Green 2011). No subgroup analysis was predetermined. We only used the data analysed in the trial for analysis in cases of missing data due to withdrawals or drop-outs. Heterogeneity between comparable trials was assessed using a standard Chi^2 test and I^2 statistics. When Chi^2 resulted in a p value < 0.1, statistically significant heterogeneity was considered present. When $I^2 > 60\%$ substantial heterogeneity was considered present (Higgins and Green 2011). We planned to analyse the potential for publication bias by examining funnel plots in the case of sufficient pooled data.

RESULTS

The search found 5442 records, of which 712 were duplicates. Of the 4730 records screened by title and abstracts, 106 were potentially relevant and full reports obtained and screened. Of these, 72 reports were excluded with reasons. Thus, there were 34 reports of studies that met our eligibility criteria and were included for review (supporting material Figure S1). Twenty-three studies were categorised as including a sample of individuals with clinical pain (607 participants). Three of these clinical studies included a sample of pain-free healthy participants that were not exposed to experimentally-induced pain (Daenen et al. 2012a; Daenen et al. 2012b; McCabe et al. 2007). These studies were included only in the analysis of clinical pain studies. Two clinical studies included a sample of pain-free healthy participants that were exposed to experimentally-induced pain (De Kooning et al. 2017; Diers et al. 2013), and were included in the analysis of clinical pain and the analysis of experimentally-induced pain in pain-free participants. Thus, 13 studies were categorised as including a sample of pain-free individuals exposed to experimentally-induced pain (310 participants).

Studies investigating participants with a clinical pain condition

Characteristics of included studies

Twenty-three studies (607 participants) were included for review (Table 1). Nine were randomised controlled trials, one randomized cross-over experiment, and three within-subjects repeated-

measures design experiments with a primary aim to evaluate the clinical efficacy of mirror VF. Three studies with a within-subjects repeated measures design used mirror VF to investigate whether visually-mediated incongruence between sensory feedback and motor output evoked pain. Six clinical studies investigated the effects of other VF techniques on pain. Study sample sizes were between 6 to 80 participants with group (trial arm) sizes between 6 to 41 participants. The characteristics of participants of each individual study (clinical condition, age, sex) are presented in Table 1.

[Insert Table 1 here]

Risk of bias

All studies had a high or unclear risk of bias associated with blinding of participants (supporting material Table S2). The outcome assessor was not blinded in 6 (23%) studies, and it was unclear whether the assessor was blinded in 10 (43.4%) studies. A sample size calculation was not reported in 9 studies (39%). Five (41.6%) of the studies with a repeated-measures design adequately controlled for crossover effects.

Analysis of mirror VF

Seventeen studies used mirror VF. Fourteen studies investigated the effects of mirror VF using a normal-sized reflection of a body part on clinical pain. Three studies investigated the presence of sensations (i.e., pain, tightness, tiredness, weight changes) whilst participants performed congruent and incongruent arm movements while looking at a normal-sized reflection of the arm.

Data for pain intensity could be pooled from 10 trials. Three studies did not measure pain intensity (Daenen et al. 2012a; Daenen et al. 2012b; Dohle et al. 2009), and the other four studies did not report all relevant information needed for analysis (Bayon-Calatayud et al. 2016; Cacchio et al. 2009a; Hunter et al. 2003; McCabe et al. 2007). Data from 6 trials comparing mirror VF using a normal-sized reflection of a body part against a no-reflection control could be analysed and resulted in a significant effect in favour of mirror VF using a random-effects model (Z=2.35, p=0.02; Figure 1(a)). The MD was -13.07 (95%CI=-23.97, - 2.17) mm on a 100mm VAS, which is considered clinically relevant. However, there was substantial heterogeneity (I^2=78%).

[Insert Figure 1 here]

A subgroup analysis was conducted comparing mirror VF using a normal-sized reflection of a body part with covered mirror control. Data for pain intensity were pooled from 3 trials and resulted in no significant overall effect (Z=1.78, p=0.08) (supporting material Figure S2(a)).

Subgroup analyses were conducted in studies in which mirror VF was delivered in one session and as a prolonged treatment. When mirror VF was administered in one session there was no significant overall effect (Z=1.03, p=0.30, supporting material Figure S2(b)). The analysis including 5 trials in which mirror VF using a normal-sized reflection of a limb was delivered in multiple sessions resulted in a significant overall effect (Z=2.20, p=0.03), but with substantial heterogeneity (I^2 =76%). The MD was -12.76 (95%CI=-24.11, -1.40) mm on a 100mm VAS using a random-effects model (Figure 1(b)).

Data from studies investigating patients with PLP and CRPS could be pooled and analysed separately. Data for pain intensity were pooled from 3 trials investigating PLP patients and resulted in no significant overall effect (Z=1.00, p=0.32, supporting material Figure S2(c)). Data for pain intensity were pooled from 3 trials investigating CRPS patients and resulted in a significant large effect in favour of mirror VF using a normal-sized reflection (Z=6.34, p<0.001 SMD=-1.44; 95%CI=-1.88, -0.99) The I^2 statistic (55%) suggested moderate heterogeneity using a random-effects model (Figure 1(c)).

A funnel plot was created to analyse publication bias (supporting material Figure S3) but there is an insufficient number of trials to allow a meaningful conclusion. Publication bias cannot be discounted.

Two studies could not be included in the meta-analysis. A study using 15 amputees with PLP showed no significant pain reduction comparing mirror VF using a normal-sized reflection with no treatment (SMD=-0.08; 95%CI=-1.10, 0.93, (Anghelescu et al. 2016). The study including 6 amputees with PLP showed that the combination of mirror VF using a normal-sized reflection with synchronised stroking of the stump and the hand in front of the mirror significantly reduced pain compared with only mirror VF using a normal-sized reflection (SMD=-1.58, 95%CI=-2.50, -0.66, (Schmalzl et al. 2013).

Follow up data from two studies were pooled. There was a significant large effect in favour of mirror VF using a normal-sized reflection in a follow-up of 6 months in the study conducted by Cacchio et al. (2009a) (SMD=-1.46, 95%CI=-1.83, -1.09). The other study showed no significant effect of mirror VF using a normal-sized reflection in a follow-up of 6 months (SMD=-0.34, 95%CI=-0.75, 0.07, (Michielsen et al. 2011).

Data could not be extracted from 4 study reports. Cacchio et al. (2009b) reported that a course of 4 weeks of mirror VF using a normal-sized reflection reduced pain intensity in patients with CRPS when compared with covered mirror and mental imagery. Bayon-Calatayud et al. (2016) investigated patients with closed distal radial fracture and found no difference in pain intensity comparing mirror VF using a normal-sized reflection with direct view of the arm. Hunter et al. (2003) investigated whether mirror VF associated with tactile stimulation was more effective than mirror VF on its own in 13 amputees. It was found that 2 participants reported pain during mirror VF, whilst no participants reported pain during mirror VF combined with tactile stimuli. McCabe et al. (2007) investigated the effect of sensory-motor mismatch in patients with fibromyalgia by asking patients to perform congruent and incongruent movements while observing the reflection of a limb or observing a white board. When observing a mirror reflection of the limb, 6 participants reported pain during congruent movements and 9 participants reported pain during incongruent movements. When observing a whiteboard 9 participants reported pain during congruent movement and 11 participants reported pain during incongruent movements.

Analyses of other VF techniques

Six of the twenty-three clinical studies evaluated other VF techniques. Differences in study designs, VF techniques and controls prevented meta-analysis. Studies were individually analysed and effects sizes calculated for comparisons within each study (Figure 2).

[Insert Figure 2 here]

Contradictory findings in primary studies meant that it was not possible to determine whether normal-sized, magnified and minified VF of body parts affected pain perception. Two studies analysed the effect of visually distorting the size of a painful hand on pain perception. One study found that minifying the affected hand significantly decreased movement-induced pain while magnifying the affected hand significantly increased movement-induced pain (Moseley et al. 2008). The other study found that shrinking and/or stretching the painful joint significantly reduced pain compared with shrinking and/or stretching the non-painful joint (Preston and Newport 2011). Four studies investigated the use of real-time video of the back of patients with chronic back pain (Diers et al. 2015b; Diers et al. 2013; Trapp et al. 2015) and whiplash-associated disorders (De Kooning et al. 2017). Studies indicated that providing normal-sized VF of the back alleviated pain at rest and during movement, but not when pain was evoked using a pressure algometer (Figure 2 and Table S3).

Studies investigating pain-free healthy subjects exposed to experimentally-induced pain

Characteristics of included studies

Thirteen studies (310 participants) were included for review (Table 2). Seven studies used mirror VF, three studies used virtual reality, two studies used real-time video, and one study used lenses. Study sample sizes varied from 10 to 44 participants and group sizes from nine to 34 participants. The mean age of participants of each individual study varied from 21.6 to 54.69 years (Table 2). Subjective characteristics of pain free subjects were recorded in two studies using the Neck Disability Index, Pain Catastrophizing Scale (De Kooning et al. 2017), and Centre for Epidemiological Studies Depression Scale (Diers et al. 2013). There were no analyses investigating the effect of these subjective characteristics on experimentally-induced pain outcomes.

[Insert Table 2 here]

Risk of bias

All studies presented high risk of bias (supporting material Table S4). The outcome assessor was not blinded in two (15.3%) studies, and it was unclear whether the outcome assessor was blinded in 10 (80%) studies. A sample size calculation was not provided in any study report. Random sequence generation of conditions was reported in 11 studies (84.6%). Eight (61.5%) of the studies with a repeated-measures design adequately controlled for crossover effects.

Analysis of mirror VF

Seven studies compared mirror VF using a normal-sized reflection of a body part with a control. There was sufficient information to analyse the effect of mirror VF on pain in six studies. Due to difference in study designs, VF techniques and controls a meta-analysis could not be conducted. Studies were individually analysed and effects sizes calculated for comparisons within each study (Figure 3).

[Insert Figure 3 here]

Mirror VF vs. control

Data for pain measures could be extracted from 6 studies and there were 29 comparisons of mirror VF using a normal-sized reflection against a control. There was no significant effect of mirror VF

compared with an object view in 4 comparisons (supporting material Table S5, (Torta et al. 2015). There was no significant effect of mirror VF compared with direct view of the body part (Johnson and Gohil 2016; Torta et al. 2015). There was a significant moderate effect size in favour of mirror VF compared with the reflection of the hand of the experimenter (SMD=-0.26; 95%CI=-0.40, -0.12 (Longo et al. 2009).

There were eight comparisons of mirror VF using a normal-sized reflection of the hand against the reflection of an object in four studies. There was a significant small effect in favour of mirror VF in two comparisons in the study by Longo et al. (2009) (Experiment 1: SMD=-0.13, 95%CI=-0.25, -0.01. Experiment 2: SMD=-0.18, 95%CI=-0.32, -0.04). There was a significant moderate (SMD=-0.59; 95%CI=-0.84, -0.34) and large effect (SMD=1.01; 95%CI=0.77, 1.25) in favour of mirror VF in two studies (Longo et al. 2012; Mancini et al. 2011). The other 4 comparisons resulted in a non-significant effect (Torta et al. 2015). Data could not be extracted from the study conducted by Mancini et al. (2013) and they reported a significant reduction in pain intensity using a normal-sized mirror reflection of the limb compared with a reflection of an object.

Three studies used mirrors to magnify and minify the size of the body part. In the study conducted by Mancini et al. (2011) there was a significant moderate effect in favour of a magnified reflection compared with a normal-sized reflection (SMD=-0.34, 95%CI=-0.63, -0.05), and a small effect in favour of mirror VF using a normal-sized reflection compared with a minified reflection (SMD=0.18, 95%CI=0.01,0.37). There were no significant differences in the other 7 comparisons (Johnson and Gohil 2016; Osumi et al. 2014).

Analysis of other VF techniques

Six of the 13 included experimental studies evaluated other VF techniques. Due to differences in study designs, VF techniques, and controls a meta-analysis could not be conducted. Studies were individually analysed and effects sizes calculated for comparisons within each study (Figure 3).

Two studies used virtual reality and found that pain was reduced by observing a virtual hand moving in synchrony with the real hand, and by observing a virtual hand that was co-located with the real arm (Martini et al. 2014; Nierula et al. 2017). Two studies used real-time VF while pain was evoked by a pressure algometer applied to the participant's back. Pain thresholds were higher when participants observed a normal-sized, real-time video of the stimulus being applied to their back compared with observing a real-time video of their hand (Diers et al. 2013) or a no VF control (De

Kooning et al. 2017). Observing a magnified or minified body part did not affect pain perception. Data could not be extracted from two studies (Romano et al. 2016; Romano and Maravita 2014). Results for individual comparisons are provided in Figure 3 and Table S5.

DISCUSSION

This systematic review included 23 clinical studies and 13 experimental studies. Our meta-analysis of data from 8 clinical studies provides tentative evidence of pain reduction when mirror VF is delivered as a course of treatment, and with patients with CRPS. There was also an effect on pain reduction in favour of mirror VF using a normal-sized reflection of a body part when compared with a no reflection control. Studies that used real-time video of the back of patients with back pain found that observing a real-time video of the back alleviated back pain at rest and during movement but did not affect pressure-evoked pain. This systematic review was unable to determine whether normal-sized, magnified and minified VF of body parts affects pain perception because of contradictory findings in primary studies.

Mirror VF using a normal-sized reflection was not superior to object view or direct view of the hand on reducing experimental pain. There was no consistency in the findings from 17 comparisons from 6 studies to determine whether there were differences experimentally-induced pain between mirror VF using a normal-sized reflection of a body part and a reflection of an object, or a magnified, or minified reflection of the body part. Inconsistent results were also obtained with the analysis of virtual reality studies.

Our meta-analysis of clinical data found a MD of -13.07mm on a 100mm VAS in favour of mirror VF using a normal-sized reflection of a body part when compared with a no reflection control. Mirror VF delivered as a course of treatment resulted in a MD of -12.76mm on a 100mm VAS in favour of mirror VF using a normal-sized reflection. Mirror VF using a normal-sized reflection showed a significant large effect size on pain reduction in patients with CRPS (SMD = -1.44; 95%CI -1.88, -0.99). Our findings should be interpreted cautiously because of substantial statistical heterogeneity and high risk of bias of primary studies. Nevertheless, our findings reach a minimal threshold for clinically meaningful and are consistent with previous reviews. Bowering et al. (2013) meta-analysed data from 3 RCTs and found no effect of mirror VF using a normal-sized reflection of body parts on pain. Thieme et al. (2016) meta-analysed data from 9 RCTs and found a significant effect of mirror VF using a normal-sized reflection of a limb on pain reduction. Boesch et al. (2016) conducted a meta-

analysis of two RCTs, and found that a 4 week course of mirror VF using a normal-sized reflection of body parts reduced pain, but a meta-analysis of 3 studies analysing one session of mirror VF did not. Substantial statistical heterogeneity was present in all of these meta-analyses. Our meta-analysis extends these findings by including three additional clinical studies.

We used broad inclusion criteria to improve statistical power but at the expense of substantial statistical heterogeneity, with studies having a high risk of bias affecting the credibility of effect sizes. Small sample sizes and underpowered primary studies were the norm, with sample size calculations provided in only 40% of clinical studies and none of the experimental studies. We used a random-effects model, which assumes effect sizes are a random sample drawn from a population of effect sizes, and variation is due to population variance plus sampling error (Borenstein et al. 2009; Higgins and Green 2011). We estimated mean and standard deviation from median, range and sample size for the RCT conducted by Vural et al. (2016) because this approach has been extensively used in previous meta-analyses and unlikely to introduce inaccuracies into statistical estimates (Bland 2015; Hozo et al. 2005; Koenig and Thayer 2016). We chose to include a variety of painful conditions and body parts as determined by the investigators of primary studies, with no reason to suspect that any of the conditions would not respond to VF.

The inclusion of several control conditions also contributed to statistical heterogeneity when one type of control dominated the analysis and when controls had varying degrees of influence. Three studies had confidence intervals that did not bisect the line of no difference and two studies found that mirror VF using a normal-sized reflection was superior to a covered mirror control (Cacchio et al. 2009a; Chan et al. 2007). Interestingly, our subgroup analysis failed to detect a significant difference between mirror VF using a normal-sized reflection and a covered mirror control, with substantial statistical heterogeneity being present. The selection of an ‘authentic’ control condition is challenging. A covered mirror is an intuitive choice for a control condition in studies evaluating mirror VF as it isolates the ‘active ingredient’ of the intervention, i.e., reflection of the body part. However, participants dismiss a covered mirror as not credible so investigators have used the reflection of an object. True blinding of participants to these control interventions and conditions is difficult with a risk of biasing outcome in favour of VF, and an overestimation of treatment effects (Bowering et al. 2013; Djavadkhani et al. 2015). Comparing mirror VF with an existing treatment does not isolate effects attributable to the ‘active ingredient’ but provides evidence to underpin treatment selection in clinical practice.

The use of broad inclusion criteria in systematic reviews has been challenged as it can lead to misleading conclusions in favour of the intervention (Carroll et al. 2000). However, this is not always the case. Bennett et al. (2011) demonstrated that potential sources of bias occur in both directions especially for treatments where the optimal technique and dosage are not known, as is the case for VF techniques. It is likely that sub-optimal VF techniques contributed to negative outcome studies. Frequency and time of exposure seems to be an important aspect of VF, and it has been recommended that mirror VF should be performed little and often. A single half hour session once a day or once a week is not encouraged (McCabe 2011). Studies included in our systematic review used a variety of VF protocols ranging from a session of 1 minute to 1 hour 5 days a week during 6 weeks. Visually distorting the size of painful body parts is another component of optimal technique that has aroused interest, despite few available studies on which to judge efficacy (Wittkopf and Johnson 2016). Likewise, embodiment of the viewed body part, which describes the subjective experience of having a sense of one's own body, including a sense of ownership of body parts (de Vignemont 2011; Longo et al. 2008), is considered an important determinant of outcome but rarely assessed in trials (Foell et al. 2014; McCabe 2011; Wittkopf et al. 2017).

It has been suggested that VF techniques correct disrupted mental representations of body parts by reducing dysfunctional cortical reorganisation (Foell et al. 2014; Lewis et al. 2007; Moseley et al. 2012; Ramachandran and Altschuler 2009). Mental representations of affected limbs have been modified using mirrors to create the illusion of having two healthy moving limbs to alleviate PLP (Foell et al. 2014; Ramachandran et al. 1995). The inconsistency in findings of studies evaluating the effect of distorting the size of a body part may be related to the type of condition and the type of VF needed to normalise the mental representation of the body part. Patients with CRPS frequently report feeling the affected limb bigger than the healthy limb (Lewis et al. 2007; Moseley 2005). Therefore, it may be expected that minifying the affected limb can normalise mental representation and reduce pain (Moseley et al. 2008). More studies are needed to investigate the effect of visually distorting the size of a body part in patients with different painful conditions. It is possible that the mechanisms associated to pain reduction in experimentally-induced pain in pain-free participants may differ from patients with a clinical pain, as most likely pain-free subjects do not have a disrupted mental representation of a healthy limb. However, there is a lack of imaging studies investigating cortical reorganisation when using VF techniques (Diers et al. 2010; Diers et al. 2015a; Flor et al. 2001; Foell et al. 2014).

In conclusion, it was not possible to determine whether normal-sized, magnified and minified VF of body parts affects pain perception in patients or pain-free participants because of contradictory findings in primary studies. The most likely explanation for the contradictory nature of the findings is variability in study methodology and a high risk of bias. Rather than continuing to undertake meta-analyses of many underpowered small scale studies of VF techniques it would be more appropriate to undertake one robust multi-centred RCT to determine clinical efficacy against a standard treatment or a pragmatic trial to determine effectiveness versus usual care. Such a trial should include sample sizes of >200 per treatment arm, as recommended by the Cochrane collaboration, to generate findings with sufficient confidence (and low risk of bias) to generalise to clinical practice. The likelihood of a multi-centred RCT being realised is low because funding councils do not consider these types of interventions high priority. Thus, meaningful synthesis of the findings of studies that evaluate VF techniques will continue to be descriptive.

Author Contributions

All authors contributed to conception, design, analysis and interpretation of data. The first author drafted the manuscript. All authors critically revised the article for important intellectual content. All authors gave final approval for publication.

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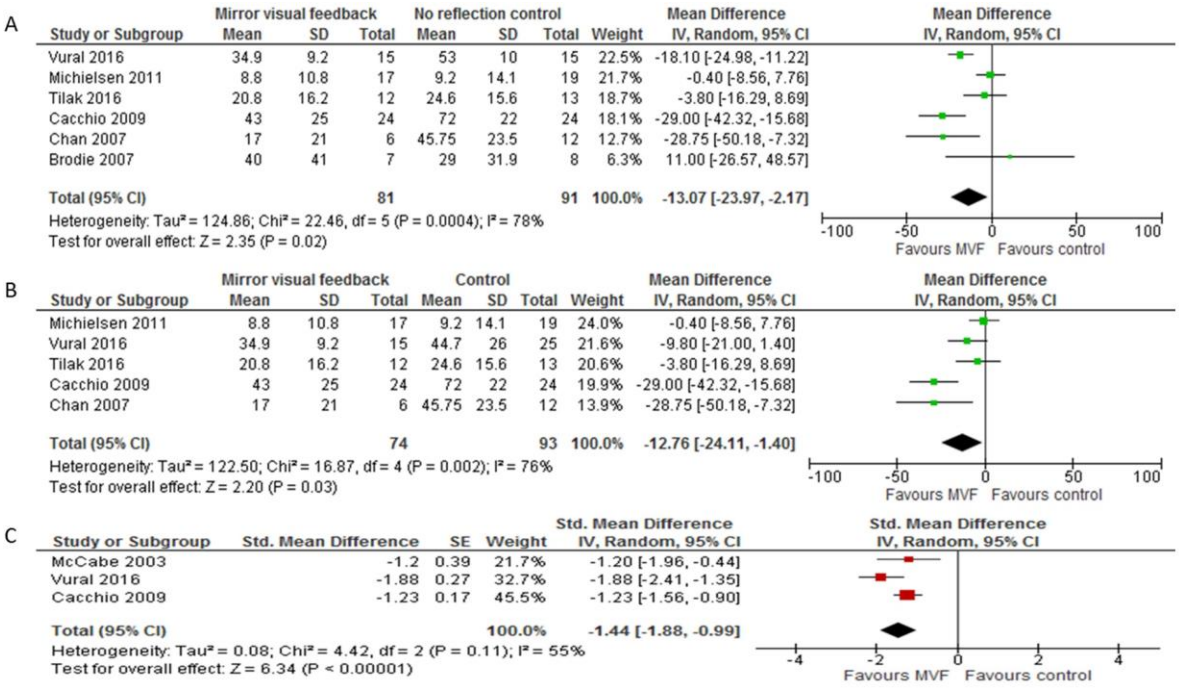

Figure 1 Forest plot of comparisons: (a) mirror visual feedback using a normal-sized reflection versus no reflection control. (b) Subgroup analysis of prolonged treatment with mirror visual feedback using a normal-sized reflection. (c) Subgroup analysis of complex regional pain syndrome patients. Outcome: Pain intensity (VAS-100mm). Abbreviation: MVF, mirror visual feedback.

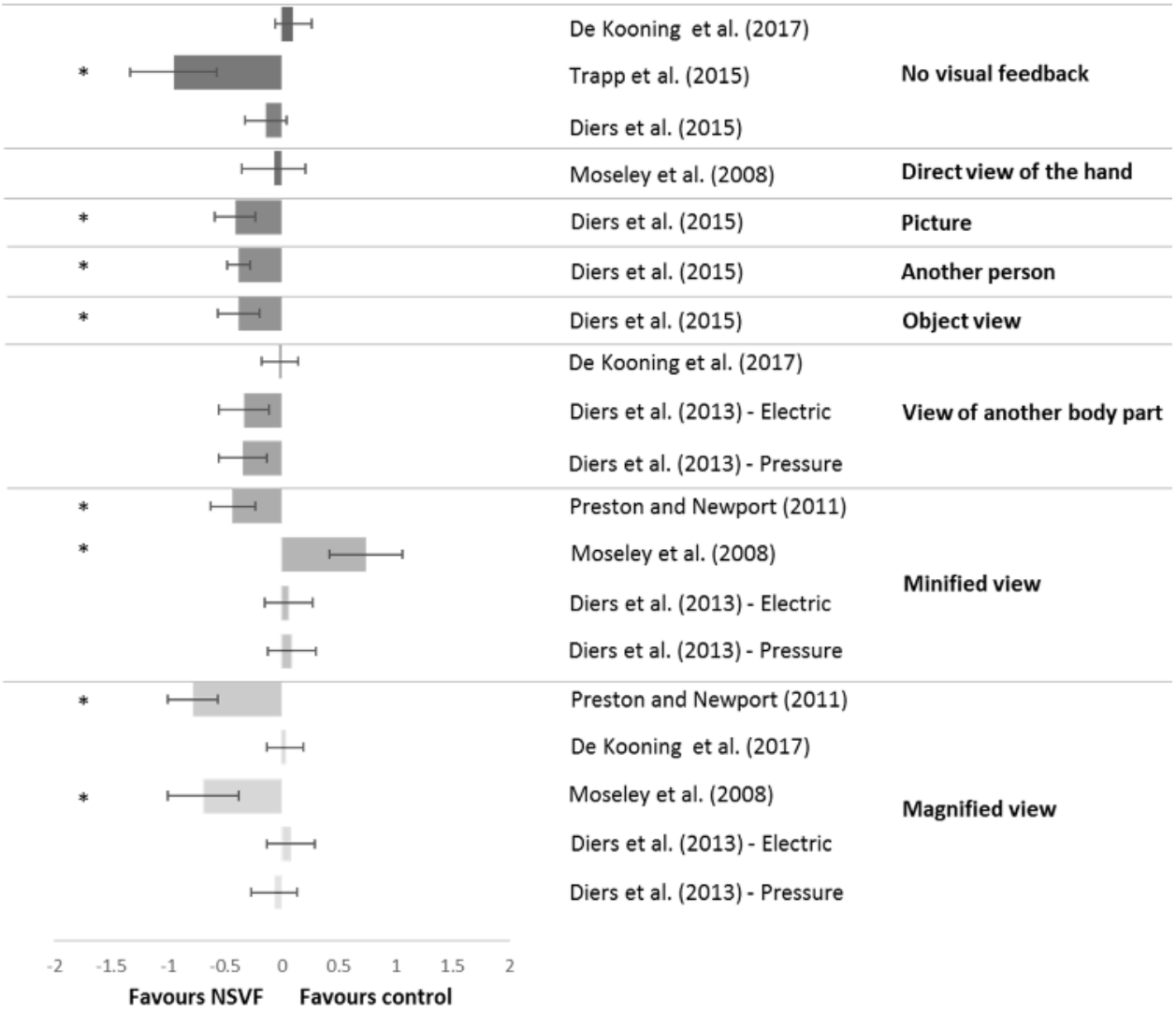

Figure 2 Effect size of comparisons of clinical studies using other visual feedback techniques. Bars represent standard mean difference and error bars represent standard error of the standard mean difference. NSVF = normal-sized visual feedback. Asterisks indicate significant effects. Results of comparisons are shown in Table S3.

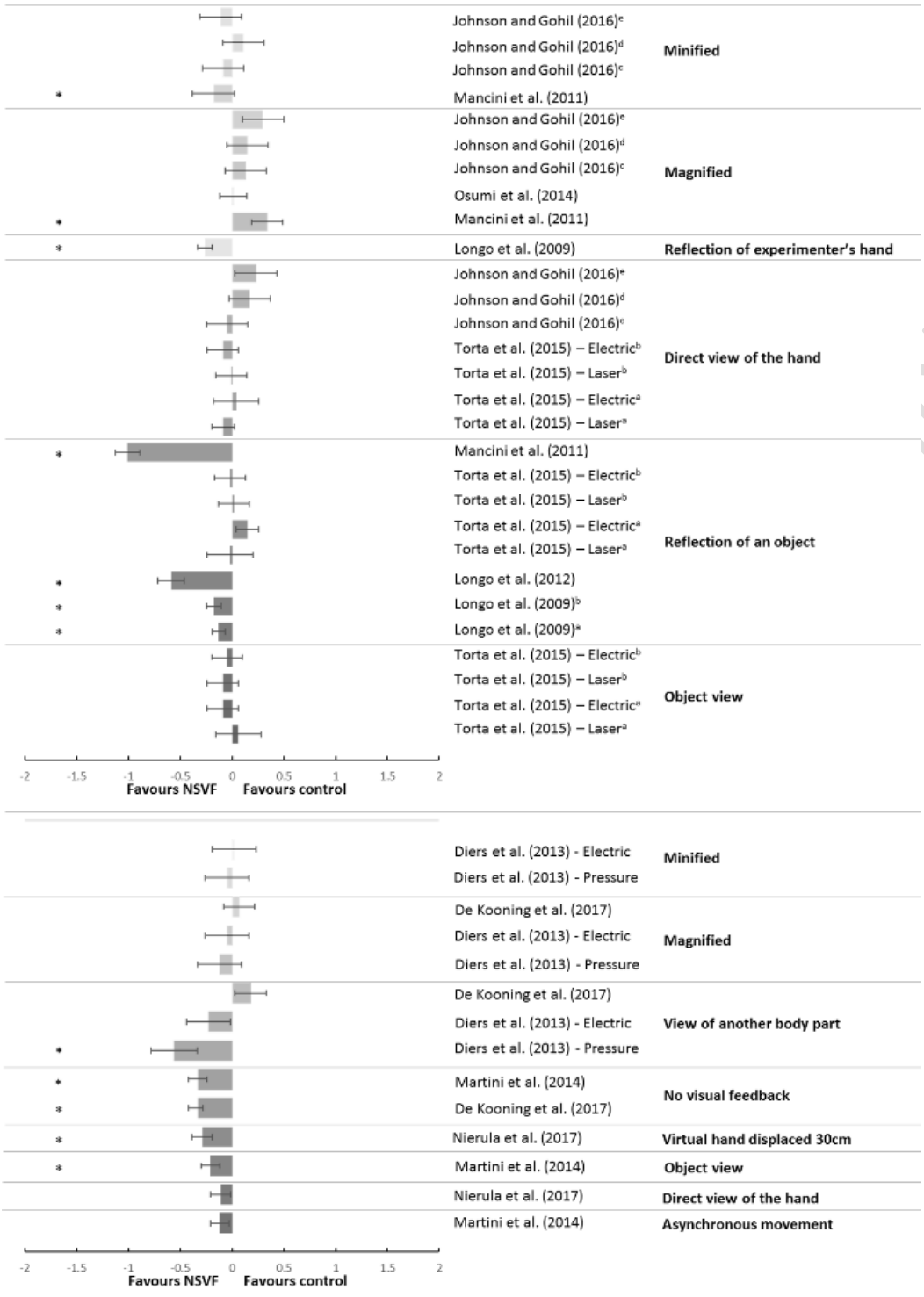

Figure 3 Effect size of comparisons of experimental studies using mirror visual feedback (top) and other visual feedback techniques (bottom). Bars represent standard mean difference and error bars represent standard error of the standard mean difference. NSVF = normal-sized visual feedback; a = experiment 1; b = experiment 2; c = pain intensity; d = pain threshold; e = pain tolerance. Results of significant comparisons are shown in the text, and non-significant comparisons are shown in Table S5.

Table 1 Characteristics of studies investigating participants with a clinical pain

Study and design	Clinical condition (total n)	Visual feedback technique	Control Group/Condition	Pain outcome measures
Normal-sized mirror visual feedback				
Michielsen et al. (2011) RCT	Stroke (36)	NSVF with a mirror (n = 17, 55.3 ± 12.0 years, 7M/13F): 6 weeks, 5 days a week, 1 hour.	Direct view of the hand (n = 19, 58.7 ± 13.5 years, 13M/7F)	Pain intensity VAS.
Cacchio et al. (2009a) RCT	CRPS type 1 (48)	NSVF with a mirror (n = 24, 57.9 ± 9.9 years, 13F/11M): First 2 weeks: 5 days a week, 30 minutes Last 2 weeks: 5 days a week, 1 hour.	Covered mirror (n = 24, 58.8 ± 9.4 years, 13F/11M)	Pain intensity VAS.
Cacchio et al. (2009b) RCT	CRPS and stroke (n = 24, median 62, range 53-71 years, 11M/13F)	NSVF with a mirror (8): 4 weeks, 7 days a week, 30 minutes.	Covered mirror (8) Mental imagery (8)	Pain intensity VAS.
Chan et al. (2007) RCT	Lower limb amputation (18, N/A)	NSVF with a mirror (6): 4 weeks, 7 days a week, 15 minutes.	Mental imagery(6) Covered mirror(6)	Pain intensity VAS.
Vural et al. (2016) RCT	CRPS type 1 (30)	NSVF with a mirror (n = 15, 68.9 ± 10.5 years, 7F/8M): 4 weeks, 5 days a week, 30 minutes.	No treatment (n = 15, 61.4 ± 11.9 years, 6F/9M)	Pain intensity VAS.
Dohle et al. (2009) RCT	Stroke (36)	NSVF with a mirror (n = 18, 54.9 ± 13.8 years, 13M/5F): 6 weeks, 5 days a week, 30 minutes.	Direct view of the hand (n = 18, 58.0 ± 14.0, years 13M/5F)	Fulgl-Meyer subscore.

Brodie et al. (2007) RCT	Lower limb amputation	NSVF with a mirror(n = 41, median 54, range 20-83 years, 35M/6F): sequence of 10 congruent movements repeated 10 times	Covered mirror (n = 39, median 57, range 25-80 years, 28M/11F)	Pain intensity VAS, McGill.
Bayon-Calatayud et al. (2016) RCT	Closed distal radial fracture (22)	NSVF with a mirror (n = 11, 61.09 ± 13.05 years, 3M/ 8F): 3 weeks, 5 days a week, 30 minutes.	Direct view of the hand (n = 11, 55.36 ± 18.28 years, 4M/7F)	Pain intensity VAS.
Tilak et al. (2016) RCT	Amputation (25)	NSVF with a mirror (n = 12, 42.62 ± 10.69 years, 12M/ 1F): 4 consecutive days, 20 minutes.	Transcutaneous electrical nerve stimulation (n = 13, 36.38 ± 9.55 years, 11M/2F)	Pain intensity VAS.
Wand et al. (2012) Randomized cross-over experiment	Chronic nonspecific low back pain (n = 25, 41.8±14.7 years, 14M/11F)	NSVF with a mirror: Participants performed movements while viewing the reflection of their low back	Covered mirror	Pain intensity VAS.
Anghelescu et al. (2011) Retrospective study	Amputation (15)	NSVF with a mirror (n = 8, median 12, range 8-20 years, 7M/1F)	No treatment (n = 7, median 26, range 10-24 years, 5M, 2F)	Pain intensity NRS.
Schmalzl et al. (2013) Within subjects repeated measures	Upper limb amputation (n = 6, 55.1 ± 14.6 years, 2M/ 4F)	NSVF with a mirror: congruent movements 60 seconds followed by 60 seconds of rest 8 times.	NSVF with a mirror plus tactile stimuli	Pain intensity VAS.
McCabe et al. (2003) Within-subjects repeated-measures	CRPS type 1 (n = 8, 33 ± 55.5 years, 5F/3 M)	NSVF with a mirror: congruent movements.	Covered mirror Mental imagery	Pain intensity VAS.

Hunter et al.(2003) Within-subjects repeated-measures	Upper limb amputation (n = 13, 36.07 ± 11.8 years, 11M/2F)	NSVF with a mirror: congruent movements.	Direct view Closed eyes NSVF with a mirror plus tactile stimuli	Pain intensity VAS.
Daenen et al. (2012a) Within and between subjects repeated measures	Acute whiplash associated disorder (n = 30, 43.30 ±10.98 years, 14F/16M)	NSVF with a mirror: congruent movements.	Within subjects whiteboard: congruent movements NSVF with a mirror: incongruent movements No mirror/whiteboard congruent movements No mirror/whiteboard incongruent movements Between subjects Healthy participants (29)	Proportion of reported sensations and intensity of sensations NRS.
Deanen et al. (2012b) Within and between subjects repeated measures	Chronic whiplash associated disorder (n = 35, 43.8 ± 9.58 years, 26F,9M)	NSVF with a mirror: congruent movements.	Within subjects whiteboard: congruent movements NSVF with a mirror: incongruent movements No mirror/whiteboard congruent movements No mirror/whiteboard incongruent movements Between subjects Healthy participants (31)	Proportion of reported sensations and intensity of sensations NRS.
McCabe et al. (2007) Within-subject repeated measures	Fibromyalgia (n = 29, 47.9 ± 11.1 years, 1M/28F)	NSVF with a mirror: congruent movements.	Within subjects comparisons whiteboard: congruent movements Normal size visual feedback with a mirror: incongruent movements Between subjects comparisons Healthy participants (29)	Proportion of reported sensations and intensity of sensations NRS.
Normal-sized visual feedback using other visual feedback techniques				

Diers et al. (2015b) Within-subject repeated measures	Chronic back pain (n = 19, 44.8 ± 17.2 years, 5M/14F)	NSVF with a real time video of their back (1minute)	Object view View of the back of another person View of the picture of their back Closed eyes	Pain intensity NRS.
Trapp et al. (2015) RCT	Chronic low back pain (30)	NSVF with real time video of their back (n = 15, 45.53 ±7.05 years, 10M/5F) 2 weeks, 3 days a week, 20 minutes	No treatment (n = 15, 40.60 ± 10.67 years, 9M/6F)	Pain intensity VAS.
Size distorted visual feedback using other visual feedback techniques				
Diers et al. (2013) Within and between subjects repeated measures	Chronic upper back pain (n= 18, 54.74 ± 9.14 years, 5M/13F)	NSVF with real time video of their back	Within subjects Magnified view of their back Minified view of their back View of the hand Between subjects healthy controls (18)	Pain intensity NRS Pain induced by pressure and electrical stimulations.
Moseley et al. (2008) Within-subject repeated measures	Chronic pain and dysfunction of one arm (n = 10, 35.1 ± 11.7 years, 5M 5F)	NSVF looking through a lens, while performing movements	Magnified view Minifed view Direct view of the hand	Pain intensity VAS.
Preston and Newport (2011) Within-subject repeated measures	Osteoarthritis (n = 20, 70.5 ± 6.5 years, 2M/18F)	Stretched and shrunken views with real time video of a painful joint	Stretched and shrunken views with real time video of a non- painful joint	Pain intensity NRS.
De Kooning et al. (2017) Within and between subjects repeated measures	Whiplash associated disorder (n = 30, 42.2 ± 10.73 years, 10M/20F)	NSVF with real time video of their neck	No visual feedback View of the hand Magnified view of the neck	Pressure pain threshold

Abbreviations: RCT, Randomised controlled trial; NSVF, Normal-sized visual feedback; VAS, visual analogue scale; CRPS, complex regional pain syndrome; NRS, numeric rating scale.

Table 2 Characteristics of studies investigating pain-free healthy participants exposed to experimentally-induced pain

Study & design	Participants (total n)	Visual feedback technique	Control Group/Condition	Pain outcome measure
Normal-sized mirror visual feedback				
Longo et al. (2009) Within subjects repeated measures	Healthy volunteers (n = 26, 24.6 ± 3.7 years, 18F/8M)	Experiment 1: NSVF of the hand with a mirror (n = 14) Experiment 2: NSVF of the hand with a mirror (n = 12)	Experiment 1: Reflection of an object. Experiment 2: Reflection of an object. Reflection of experimenter's hand	Pain intensity and unpleasantness VAS. Before and after stimulus with infrared laser.
Longo et al. (2012) Within subjects repeated measures	Healthy volunteers (n = 14, 19–44 years, 3F/11M)	NSVF of the hand with a mirror	Reflection of an object.	Pain intensity and unpleasantness NRS after stimulus with infrared laser.
Torta et al. (2015) Within subjects repeated measures	Healthy volunteers Experiment 1: n = 16, 26.2 ± 2.8 years, 7F, 9M)Experiment 2: n= 8, 27.5 ± 3.6 years, 6F/2M)	NSVF of the hand with a mirror	Direct view of the hand Object view Reflection of an object	Intensity of the perception NRS. Before and after stimulus with infrared laser and electrical stimulation.

Mancini et al. (2013) Within subjects repeated measures	Healthy volunteers (n = 10, mean 25, range 19– 32 years)	NSVF of the hand with a mirror	Reflection of an object	Pain intensity NRS during contact thermal heat stimulation
Size distorted mirror visual feedback				
Johnson and Gohil (2016) Within subjects repeated measures	Healthy volunteers (n = 20, 23.55 ± 4.01 years, 10M/10F)	NSVF of the hand with a mirror	Magnified reflection of the hand Minified reflection of the hand Direct view of the hand	Pain threshold, tolerance and intensity VAS. During cold-pressor task.
Mancini et al. (2011) Within and between subjects repeated measures	Healthy volunteers (n = 18, 27,1 ± 4,1 years, 7M/11F	NSVF of the hand with a mirror	Within subjects Magnified reflection of the hand Minified reflection of the hand Between subjects Reflection of an object	Contact heat pain threshold
Osumi et al. (2014) Within and between subjects repeated measures	Healthy volunteers (n = 44, 21.6 ± years, 17M/27F)	NSVF of the hand with a mirror	Magnified reflection of the hand	Contact heat pain threshold
Normal-sized visual feedback using other visual feedback techniques				
Nierula et al. (2017) Within subjects repeated measures	Healthy volunteers (n = 19, 24.1 ± 5.1 years, 19M)	NSVF of the arm of an avatar co-located with participants' arm	NSVF of the arm of an avatar displaced 30 cm away from participants' body midline	Contact heat pain threshold

Martini et al. (2014) Within subjects repeated measures	Healthy volunteers (n = 24, 25.5 ± 5.8 years, 14F/10M)	NSVF of an avatar index finger moving in synchrony to participants' finger.	No visual feedback Object view NSVF of an avatar index finger moving in asynchrony to participants' finger.	Contact heat pain threshold
Size-distorted visual feedback using other techniques				
Romano and Maravita (2014) Within subjects repeated measures	Healthy volunteers (n = 38, 24.46 ± 3.88, 30F/8M)	NSVF of the hand looking through a lens	Magnified view of the hand Minified view of the hand	Pain intensity VAS, after noxious stimuli with a non- invasive needle with a blunt end.
Romano e al. (2016) Within subjects repeated measures	Healthy volunteers (n = 21, 23 ± 2 years, 9F/12M)	NSVF of an avatar legs congruent with the position of participants' legs	Magnified view of the avatar's leg Minified view of the avatar's leg	Pain intensity VAS, after noxious stimuli with a non- invasive needle with a blunt end.
De Kooning et al. (2017) Within and between subjects repeated measures	Healthy controls (n = 34, 44.59 ±13.85 years, 11M/23F)	NSVF with real time video of their neck	No visual feedback View of the hand Magnified view of the neck	Pressure pain threshold
Diers et al. (2013) Within and between subjects repeated measures	Healthy volunteers (n = 18, 54.69 ± 9.09 years, 6M/12F)	NSVF with real time video of their back	Within subjects Magnified view of their back Minified view of their back View of the hand	Pain intensity NRS Pain induced by pressure and electrical stimulations.

Abbreviations: NSVF, Normal-sized visual feedback; VAS, visual analogue scale; NRS, numeric rating scale.