The effectiveness of hypnosis for pain relief: A systematic review and meta-analysis of 85 controlled experimental trials

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Number of manuscript pages: 29

Number of figures: 3

Number of tables: 2

Online supplementary material: 2 (search strings and study validity ratings)

Word count (exc. abstract, references, tables): 4803

Declaration of interest

Declarations of interest: none

ABSTRACT

The current meta-analysis aimed to quantify the effectiveness of hypnosis for reducing pain and identify factors that influence efficacy. Six major databases were systematically searched for trials comparing hypnotic inductions with no-intervention control conditions on pain ratings, threshold and tolerance using experimentally-evoked pain models in healthy participants. Eighty-five eligible studies (primarily crossover trials) were identified, consisting of 3632 participants (hypnosis *n*=2892, control *n*=2646). Random effects meta-analysis found analgesic effects of hypnosis for all pain outcomes (*g*=0.54-0.76, *p'*s<.001). Efficacy was strongly influenced by hypnotic suggestibility and use of direct analgesic suggestion. Specifically, optimal pain relief was obtained for hypnosis with direct analgesic suggestion administered to high and medium suggestibles, who respectively demonstrated 42% (*p*<.001) and 29% (*p*<.001) clinically meaningful reductions in pain. Minimal benefits were found for low suggestibles. These findings suggest that hypnotic intervention can deliver meaningful pain relief for most people and therefore may be an effective and safe alternative to pharmaceutical intervention. High quality clinical data is, however, needed to establish generalisability in chronic pain populations.

Keywords: pain; hypnosis; analgesia; review; meta-analysis; suggestion

1 INTRODUCTION

Pain affects up to 1.5 billion adults worldwide (Yaqub, 2015) and has a substantial negative impact on quality of life. In addition to becoming one of the leading causes of years lived with disability (GBD Causes of Death Collaborators, 2017), pain also incurs a massive economic burden. Pain-related health care and lost productivity incur annual costs of up to $635 billion in the US alone (Gaskin and Richard, 2012), greater than that of heart disease, cancer or diabetes. Increasing concern over the side effects, addictive properties and costs of opioid medication has led to an urgent need to identify non-pharmacological interventions for pain that are effective, safe, and inexpensive.

One popular psychological intervention for pain management is hypnosis, which typically involves relaxation, focused attention and targeted verbal suggestion to alter perceptual experience and behaviour (Jensen and Patterson, 2014). Hypnosis is easily administered, has few or no side effects, and is inexpensive if delivered in a pre-recorded format (e.g., audio recording) that does not require the presence of a practitioner (Jensen et al., 2015). Recent research has indicated that hypnotic suggestion produces altered activity in key regions of the brain involved in pain regulation, including the anterior cingulate, prefrontal and insular cortices (Del Casale et al., 2015), and this could provide a basis for possible analgesic effects. Exaggerated claims of hypnotic analgesia have, however, created scepticism over its efficacy (Larkin, 1999), and a rigorous evaluation of controlled trials is needed to properly evaluate and quantify its effectiveness for reducing pain.

A recent meta-analysis of 14 trials of people with chronic pain (Adachi et al., 2014) concluded that hypnosis was effective for managing pain. However, this conclusion was based primarily on a subset of 4 studies comparing hypnosis with standard care ($d=.60$, $CI_{95}[0.03, 1.17]$) that was largely unreplicated in other subset comparisons. Individual study findings were inconsistent, probably resulting from variation in pain conditions, control comparisons (e.g. treatment-as-usual, no intervention) and hypnotic suggestibility of study samples, and thus this meta-analysis provides an

unclear overall picture of the analgesic benefits of hypnosis. Other reviews have indicated beneficial effects of hypnosis on labour pain (Madden et al., 2016), and fibromyalgia (Bernardy et al., 2011), but have all concluded that supporting clinical evidence is of low methodological quality.

The effect of hypnosis on pain has also been examined using experimental paradigms to provide a level of methodological control difficult to achieve in clinical settings. A meta-analysis of 18 studies that included 12 experimental and 6 clinical trials (Montgomery et al., 2000) found significant moderate analgesic effects of hypnosis (d=.67). While this represents an important finding, several important limitations driven primarily by a lack of available data should be noted. First, determining the level of *meaningful* analgesia from hypnosis is difficult given the absence of a metric on which meaningful clinical change can be mapped (e.g. 0-10 numerical ratings). Second, estimates of hypnotic analgesia were complicated by considerable heterogeneity in control comparators. Third, factors such as hypnotic suggestibility and the use of direct analgesic suggestion that may be critical to treatment success (Patterson and Jensen, 2003) could not be adequately assessed. A large number of experimental studies have been published since this meta-analysis from almost 20 years ago, thereby providing a new opportunity for more reliable estimates of the effectiveness of hypnosis for pain reduction and to assess potential moderating factors.

To fill the gap in current knowledge regarding the efficacy of hypnosis for pain, we conducted a meta-analysis comparing hypnotic interventions with no-treatment control in studies using experimental pain models in healthy participants. Specific aims were to obtain precise estimates of: (1) the magnitude of hypnotic analgesia on standardized and unstandardized scales (e.g. 0-10 ratings); and (2) the degree to which intervention effectiveness is dependent upon both hypnotic suggestibility and the inclusion of direct suggestions of pain relief.

2 METHOD

This systematic review was conducted in accordance with the PRISMA-P 2015 statement for systematic review and meta-analysis protocols (Moher et al., 2015). An *a priori* but unpublished protocol was followed (available from the authors upon request).

2.1 Eligibility Criteria

Inclusion criteria were: (1) a hypnotic induction; (2) a non-hypnosis control condition with no active intervention; (3) an experimental pain stimulus administered to healthy participants; and (4) a quantitative assessment of pain. Although there is no established consensus for a definition of a hypnotic induction (Terhune and Cardeña, 2016), we used the conceptualisation by Jensen and Patterson (2014) of suggestions offered to another person to alter perceptual experience and voluntary action that typically involves relaxation, focused attention and/or imagery. Exclusion criteria were: (1) hypnosis induced by a pharmacological agent (e.g. ketamine); or (2) co-administration of hypnosis with other intervention(s).

2.2 Search Strategy

PubMed, EMBASE, PsycINFO, CINAHL, CENTRAL and Web of Science databases were searched independently by two reviewers (RR, JS) for potentially eligible studies indexed from database inception until 21st May, 2018.

The search string consisted of three elements related to hypnosis AND pain AND experimental noxious stimuli (see Appendix S1). Specific free text words chosen for experimental pain methods were derived from Gracely (2005) and our previous meta-analyses (Thompson et al., 2017a; Thompson et al., 2017b). Searches were applied to all database fields where possible, or title/abstract/keywords where this restriction was imposed by the database. Results were limited *a posteriori* to 'human studies' and searches were augmented through manual searches of reference lists of included articles and reviews.

2.3 Study selection

Titles and abstracts of articles returned by initial searches were independently screened by two reviewers (RR, JS) who rejected articles not meeting eligibility criteria. The full-text of remaining articles was independently examined by the same reviewers to reach a final list of articles. Disagreements at either screening stage were resolved through discussion with a third reviewer (TT). When an eligible article provided insufficient data for inclusion, corresponding authors were contacted up to 3 times over an 8-week period to request additional data. Of 20 author groups contacted, 6 (30%) provided data sufficient to permit study inclusion (see acknowledgements section).

2.4 Pain outcomes

Outcome variables were: (1) self-reported pain ratings (e.g. 0-10 rating scale), (2) pain tolerance and (3) pain threshold. Pain threshold is the point at which pain is first detected and tolerance is the point at which pain can no longer be endured, with both measures typically quantified as stimulus intensity (e.g. temperature) or exposure time.

Pain ratings were included to provide a clinically meaningful measure of pain, with threshold and tolerance included as they represent behavioural responses to minimal and maximal pain respectively.

2.5 Study quality

Two raters (RR, JS) independently rated each study for methodological quality on a 15-item validity scale assessing methodological rigour, selection and reporting bias (Table S1). Items were based on Cochrane criteria and PRISMA recommendations, and were adapted from Thompson et al. (2017a) for the current review.

2.6 Data Extraction

Extraction and coding of study data were performed by three authors (CO, RR, JS) on a standardized template (Thompson et al., 2017a), with all data entry checked by

another reviewer (TT). The following data were extracted: (1) pain outcomes; (2) sample characteristics: age, gender, hypnotic suggestibility; (3) study characteristics: location, design, pain induction method; (4) hypnotic induction: method (e.g. Stanford procedure), format (e.g. verbal, virtual reality), direct suggestions of analgesia (present, absent), number/duration of sessions, control condition (nothing, placebo). For pain outcomes, when a study did not report *M*s and *SD*s, effect sizes were calculated from any other statistics that allowed their computation based on standardised formulae (Cooper et al., 2009).

When a study provided data for multiple effect sizes (e.g. across different time points), all such data were extracted. In addition, the following extraction decisions were made: (1) for a few studies that did not report *M*s/*SD*s but did report significance thresholds (e.g. $p<.01$), we conservatively rounded these to absolute *p*-values (e.g. $p=.01$) to compute effect size; (2) for a few studies that reported use of hyperalgesic (pain increasing) and analgesic suggestions across different hypnotic conditions, only analgesic data were extracted; (3) data from a few studies ($k=3$) that used control conditions involving reading, relaxation or a simple cognitive task were included, as although not entirely inactive, these were considered unlikely to have substantial analgesic effects; (4) for a few studies ($k=5$) that collected pain ratings using a tolerance model (where stimulus intensity/exposure time can potentially vary across groups), pain outcome data were included. This was a conservative strategy, as all studies reported longer exposure times for hypnosis, so pain ratings in this condition would not be expected to be reduced due to the use of a tolerance model. For (1), (3) and (4), sensitivity analyses were conducted to examine their impact on effect size.

2.7 Hypnotic suggestibility

Hypnotic suggestibility is the degree of responsiveness to suggestions made within a hypnotic induction. Scoring is typically based on the aggregation of behavioural responses to a series of individual suggestions (e.g. whether suggestions of heaviness or tiredness in the arm produce lowering of the hand by 6 inches or more)

(Weitzenhoffer and Hilgard, 1962). Study samples were classified as low, medium or high in hypnotic suggestibility if scores on standardised measures fell within the following ranges: (a) Harvard Group Scale of Hypnotic Suggestibility:Form A (HGSHS:A) and Stanford Hypnotic Suggestibility Scale (SHSS) forms A and C: low (0-4), medium (5-7), high (8-12) (Shor and Orne, 1963; Weitzenhoffer and Hilgard, 1962); (b) Carleton University Responsiveness to Suggestion Scale: Objective dimension (CURSS:O): low (0-2), medium (3-4), high (5-7) (Spanos et al., 1983b); and (c) Stanford Hypnotic Arm Levitation Induction and Test (SHALIT): low (0-3), medium (4-7), high (8-12) (Hilgard et al., 1979).

Classifications were made using two different methods. First, a study sample was classified as low, medium or high suggestibility if the reported study range fell within the above normative boundaries (*k*=40). Second, as sometimes only mean scores were reported or ranges did not precisely match normative ranges, we used an alternative, less stringent classification to maximise study inclusion (*k*=67) for moderation analysis. Specifically, we made additional classifications when (a) the *mean* suggestibility score fell within normative boundaries (and range was not reported), or (b) reported study ranges closely approximated normative guidelines (e.g. when 0-5, rather than 0-4, was reported for the Stanford scale). We employed the less stringent classification in moderation analysis, but performed sensitivity analysis to evaluate the impact of this decision.

2.8 Effect size

The standardized mean difference (*SMD*) for hypnosis vs. control was computed with Hedges' *g* formula (Cooper et al., 2009), where 0.20, 0.50 and 0.80 can be broadly translated as small, medium and large effects (Cohen, 1988). *SMD*s for all studies were computed using original (unadjusted) standard deviations, but effect size variance was computed dependent upon study design (Morris and DeShon, 2002). Effect sizes were coded so that positive values indicated beneficial effects of hypnosis (i.e. a decrease in pain ratings or an increase in threshold/tolerance).

2.9 Meta-analysis

A random-effects model was used as heterogeneity in effect size due to variation in study methodology is likely. As studies typically report multiple effect size data (e.g. from the same subjects across multiple time points), we used a robust variance estimation (RVE) method (Hedges et al., 2010) to account for within-study dependency of effect sizes. In RVE, individual weights are based on the true common correlation of within-study effect sizes. Although this value is usually unknown, simulation studies have shown that different correlations tend to have little impact on results (Tanner-Smith and Tipton, 2014; Hedges et al., 2010). We used r=0.65 as our estimated correlation as this approximated that typically reported by studies employing repeated testing, but conducted sensitivity analysis using lower (r=.40) and higher (r=.90) correlations to examine the effect on parameter estimates. RVE meta-analysis estimates are most reliable when 10 or more studies are available (Tanner-Smith and Tipton, 2014). A few studies collected pain ratings on scales other than 0-10 (e.g. 0-20), and these were transformed to a 0-10 scale.

2.10 Meta-regression

RVE meta-regression analyses were performed to identify potential sources of heterogeneity size if moderate or greater inconsistency was found, as indicated by I^2>50% (Higgins et al., 2003) and 40 or more studies were available (Tanner-Smith and Tipton, 2014).

Primary moderators were: (1) hypnotic suggestibility (low/medium/high), and (2) direct analgesic suggestion (present/absent), with the hypothesis that hypnosis would produce greater analgesia when participants were higher in hypnotic suggestibility and direct suggestions of pain relief were present.

Secondary moderators were examined to provide preliminary data on any moderating influence of hypnosis method, format (audio recording/live), comparison group (control/placebo), study age, gender composition and pain induction method. Where the endorsement of important study validity criteria varied across studies,

the influence of these criteria as potential moderators of effect size was also assessed.

2.11 Publication bias

To assess potential publication bias, funnel plots of average study effect sizes against standard errors were examined for asymmetry resulting from a relative lack of small studies with small effect sizes (i.e. those most likely to be non-significant and remain unpublished). Asymmetry was also tested statistically with Egger's bias test (Egger et al., 1997) with $p<.05$ indicating asymmetry. If evidence of asymmetry was present, a revised effect size was computed using the trim and fill method (Duval and Tweedie, 2000).

All analyses were performed using the *robumeta* (Fisher and Tipton, 2014) and *metafor* (Viechtbauer, 2010) packages in R (R Core Team, 2017).

3 RESULTS

3.1 Study inclusion

An initial pool of 4,801 unique studies were identified through database searches, with 14 additional records acquired through manual searching of reference lists. Screening of titles/abstracts identified 229 potentially eligible articles, with full-text review resulting in a final list of 85 eligible studies (see Figure 1). Key characteristics of these studies are presented in Table 1.

3.2 Participant characteristics

The 85 studies provided data for 3,632 participants (hypnosis n=2,892, control n= 2,646, with crossover trials primarily used). Mean study age (reported by k=28 of 85 studies) was 24.6 years (SD=4.5) for hypnosis and 25.4 years (SD =4.4) for controls.

Mean gender composition (*k*=62) was 63.5% female (*SD*=22.4) for hypnosis and 63.1% female (*SD* =23.8) for controls.

3.3 Study characteristics

Study designs used were crossover (*k*=61), pre-post control (*k*=22) and parallel groups (*k*=2). Study locations were USA (*k*=32), Italy (*k*=16), Canada (*k*=15), Germany (*k*=4), UK (*k*=3), France (*k*=3), Belgium (*k*=3), Denmark (*k*=2), Israel (*k*=2), Netherlands (*k*=1), Australia (*k*=1), New Zealand (*k*=1), Romania (*k*=1) and Switzerland (*k*=1).

3.4 Pain assessment and induction

Different pain assessment (*k*s: intensity ratings=66, affective ratings=24, tolerance=18, threshold=16) and pain induction (*k*s: cold=23, electric=22, pressure=19, heat=16, ischemic=5, laser=2) methods were used, with multiple assessment and induction methods within a single study sometimes employed. Noxious stimuli were most commonly applied to the hand (*k*=62) or forearm/upper arm (*k*=12).

3.5 Hypnotic induction and suggestibility

Details of hypnotic induction procedures are provided in Table 1, which we broadly categorised as standard/typical hypnotic procedures (*k*=55) and standardized (e.g. HGSHS/SHSS) inductions (*k*=30) (both procedures typically include combinations of eye fixation, progressive relaxation and suggestions of drowsiness). Direct analgesic suggestions (e.g. 'you cannot feel pain because the glove you are wearing prevents you from feeling it') were present (*k*=72) and/or absent (*k*=37) and hypnosis was delivered in several formats (*k*s: live=68, recorded audio=19, virtual media=3). Comparison conditions consisted of an inactive control (*k*=83) and/or a placebo condition (*k*=8) such as a sham analgesic spray.

Hypnotic suggestibility was assessed in 78 studies primarily using the SHSS (*k*=35; form C=28, form A=7), HGSHS:A (*k*=23), CURSS:O (*k*=19), SHALIT (*k*=2) and/or WSGC

(*k*=2) tests. Most studies used a single session of hypnosis (*k*=74), with a small subset using two (*k*=10) or three sessions (*k*=1) with sessions usually lasting 15-30 mins.

3.6 Study validity criteria

Study ratings for each validity criteria are shown in Appendix S2. Although most study criteria were well met, several criteria were not. Perhaps most importantly, only 42% of studies explicitly reported random allocation/counterbalancing. More specifically, 18/24 (75%) parallel/pre-post control designs reported random group allocation, and only 18/61 (30%) crossover studies counterbalanced/randomised presentation order, with control procedures typically occurring first. As this could potentially result in bias from habituation or sensitisation to repeated pain stimulation, the impact of randomisation vs. non-randomisation on effect size was examined in moderation analysis. Only a few studies screened participants for pre-existing pain (18%) or gave details on use of pain medication (25%), although these would seem less likely to present serious threats to overall conclusions given the primary use of crossover designs.

3.7 Rater agreement

For study selection, good rater agreement was shown at the full-text review stage (95% agreement, kappa=.80), with initial discrepancies primarily due to uncertainty over control group eligibility. For ratings of validity criteria, acceptable agreement was demonstrated for the majority of the individual items (agreement=77-99%; kappa=0.45-0.92) with agreement lowest for adequacy of control group description (77%) and recruitment procedures (83%). In all cases of disagreement, 100% consensus was reached after discussion with a third reviewer (TT).

3.8 Outliers

Studentized residuals>3.3 from initial meta-analysis (Viechtbauer and Cheung, 2010) suggested one potential outlier for tolerance (Casiglia et al., 2007), one for pain affect (Price and Barber, 1987) and two for pain intensity (Faymonville et al., 2003; Crawford et al., 1993). Although no obvious reason for these outlying values could

be identified from further scrutiny of these papers, these cases were conservatively removed to prevent potential distortion of results (as these were all high positive values, removal resulted in marginally reduced, rather than inflated, effect sizes).

3.9 Meta-analysis

3.9.1 *Pain ratings: Intensity*

Meta-analysis of 64 studies (205 effect sizes) of pain intensity across 3,039 participants (hypnosis *n*=2,366, control *n*=2,168), found hypnosis to result in lower overall pain intensity, *SMD*=0.74, CI_{95}[0.63, 0.84], *p*<.001 (Figure 2), classifiable as a large effect (Cohen, 1988). Positive effect sizes were found in all but one study, but with high inconsistency in magnitude (I^2=75%).

Analysis of 52 studies which provided raw, unstandardized 0-10 ratings were consistent with these results (Mean Difference=1.49, CI_{95}[1.21, 1.78], *p*<.001). A decrease from 5.5 to 4.0 points was observed with hypnosis, a reduction of around 27% or 1.5 points.

3.9.2 *Pain ratings: Affect*

Meta-analysis of 23 studies (103 effect sizes) of 751 participants (hypnosis *n*=665, control *n*=587) revealed similarly lower affective pain ratings for hypnosis, *SMD*=0.76, CI_{95}[0.53, 0.99], *p*<.001. High inconsistency in effect size was observed (I^2=78%), although positive effect sizes were observed for all 23 studies. Analysis of unstandardized 0-10 pain affect ratings from 18 studies indicated a mean reduction of 1.53 points, CI_{95}[1.14, 1.93], *p*<.001, for hypnosis.

3.9.3 *Pain tolerance*

Meta-analysis of 17 studies (33 effect sizes) of 696 participants (hypnosis *n*=536, control *n*=470) indicated higher tolerance (i.e. reduced pain) for hypnosis, *SMD*=0.54, CI_{95}[0.38, 0.70], *p*<.001. Positive effects were indicated in all studies, but with moderate inconsistency in effect size (I^2=56%).

3.9.4 *Pain threshold*

Meta-analysis of 16 studies (64 effect sizes) of 415 participants (hypnosis *n*=382, control *n*=380) found higher pain threshold (i.e. reduced pain) for hypnosis, *SMD*=0.66, CI_{95}[0.38, 0.70], *p*<.001. Positive effects were found for all studies, but with high inconsistency (I^2=78%).

3.10 Publication bias

Funnel plots and Egger's test suggested asymmetry in pain intensity (*z*=2.39, *p*=.017), tolerance (*z*=2.30, *p*=.022) and threshold (*z*=2.06, *p*=.039), that was consistent with possible publication bias. Trim and fill estimates produced slight reductions in effect sizes for intensity (ΔSMD=-.06; Figure 3), tolerance (ΔSMD=- .06) and threshold (ΔSMD=-.04).

3.11 Meta-regression

Meta-regression was performed for pain intensity only as study numbers (*k*=64) were considerably higher than other pain outcomes (*k*s=16-23) and thus provide more reliable parameter estimates.

3.11.1 *Primary moderators*

Analgesic suggestion (yes, no) and hypnotic suggestibility (low, medium, high) were entered simultaneously as dummy-coded moderators, with no analgesic suggestion and low suggestibility coded as reference levels. Both variables were well represented by studies across their different levels (hypnotic suggestibility: low=31, medium=15, and high=43 studies; analgesic suggestion: yes=48, no=24 studies).

Meta-regression parameter estimates are shown in Table 2 for unstandardized (0-10) ratings and indicate greater pain relief for increasing suggestibility (+0.64 for medium, +1.34 points for high) and inclusion of a direct analgesic suggestion (+0.94 points). Solving the regression equation at different predictor values revealed that relative to control pain intensity ratings of 5.5, hypnosis with direct analgesic

suggestion decreased pain by: 2.30 points (CI_{95}[1.82, 2.80], p<.001) in high suggestibles (42% reduction), 1.60 points (CI_{95}[1.23, 1.99], p<.001) in medium suggestibles (29% reduction), and 0.97 points (CI_{95}[0.61, 1.32], p<.001) for low suggestibles (17% reduction).

Hypnosis with no direct analgesic suggestion decreased pain ratings by: 1.36 points (CI_{95} [0.48, 2.28], p=.004) in high suggestibles (25% reduction), 0.67 points (CI_{95}[0.10, 1.23], p=.025) in medium suggestibles (12% reduction), and 0.03 points (CI_{95}[-0.65, 0.59], p=.931) in low suggestibles (0.5% reduction), with the latter result not significant.

3.11.2 *Secondary moderators*

Separate meta-regression was performed for the following moderators after removing levels of any variable with low (<5) study numbers: delivery format (audio recording, live), hypnotic induction method (standard procedure, standardized induction), comparison (control, placebo), pain induction (heat, electric, pressure, cold), age and study gender composition. We also examined whether randomisation vs. non-randomisation influenced effect size (Section 3.6). Results indicated hypnotic analgesia was marginally lower (ΔSMD=-.01) for studies reporting randomization (primarily of presentation order) relative to those that did not, but this was not significant (p=.90). No secondary moderators were significant (ps=.22-.85).

3.12 Sensitivity analysis

We re-ran analyses using alternative correlations of effect sizes (section 2.9), using more stringent hypnotic suggestibility classifications (section 2.7), and with extraction decisions specified in Section 2.6, but found no substantive changes in parameter estimates.

4 DISCUSSION

The effectiveness of hypnosis for reducing pain was supported by meta-analysis of 85 controlled experimental trials totalling 3,632 participants. Key findings were: (1) hypnosis produced moderate to large overall analgesia for all pain outcomes; (2) hypnotic suggestibility and the inclusion of a direct analgesic suggestion are important determinants of intervention effectiveness; and (3) possible publication bias was identified, but had minimal impact on effect sizes.

4.1 Magnitude of pain relief

Hypnosis with analgesic suggestion produced a 42% reduction in pain intensity for those with high hypnotic suggestibility and a 29% reduction for those with medium hypnotic suggestibility. This is broadly supportive of a meaningful level of analgesia based on established guidelines for clinically important change, where a ≥30% reduction in pain typically represents 'much improved' (although ≥50% reductions are needed for 'very much improved')(Dworkin et al., 2008).

Importantly, pain relief approaching or exceeding 30% was dependent upon (1) the inclusion of direct suggestion of pain relief, and (2) a target population of individuals high or medium in hypnotic suggestibility. Insofar as the majority of the general population (85-90%) fall into the medium to high hypnotic suggestibility range (McConkey, 2012), these findings suggest that most individuals are able to experience meaningful analgesia from hypnosis provided direct analgesic suggestions are included. Hypnotic suggestibility has also been shown to influence efficacy of hypnosis in clinical care settings, although a meta-analysis of 10 studies by Montgomery et al. (2011) found relatively small moderating effects and questioned the usefulness of pre-assessing hypnotic suggestibility. However, Montgomery et al. (2011) examined a broad range of medical, dental and mental health conditions that included only 3 available pain studies, and thus further data is needed before conclusions on generalisability to clinical pain contexts can be made.

4.2 Previous findings

Analgesic effects of hypnosis in experimental pain trials are consistent with a previous meta-analysis published almost 20 years ago (Montgomery et al., 2000). Due to a vastly increased number of experimental pain trials in the current (85 studies) compared to the original meta-analysis (12 studies), current findings were also able to provide precise estimates of analgesia on a more meaningful (0-10) metric. We were also able to identify hypnotic suggestibility and use of analgesic suggestion as important determinants of treatment efficacy, as has long been suspected (Patterson and Jensen, 2003). Beneficial effects of hypnosis on pain have also been supported in reviews of labour pain (Madden et al., 2016), fibromyalgia (Bernardy et al., 2011) and other pain conditions (Adachi et al., 2014), although these reviews acknowledge the low quality of methodological evidence.

4.3 Implications

The present analysis has several important implications. Hypnosis may be an effective intervention for pain that could be offered as a safe alternative to medication, especially where concerns exist for an individual over the effectiveness, addictive potential or side effects of drug treatment. If hypnosis could be administered as effectively at home (e.g., in the form of pre-recorded audio) as during live sessions with a practitioner, then this could also provide an inexpensive treatment option for pain. This would be of considerable potential benefit given that the costs of prescription opioid addiction alone are estimated at over $78 billion annually in the US (Seth et al., 2018). However, while moderation analysis found no differences in analgesia between recorded audio and live hypnosis, suggesting the former may be similarly effective, we examined delivery format only as a secondary moderator. Furthermore, we did not perform an economic analysis, and so no claims of improved cost-effectiveness relative to opioids can therefore be made from the current study.

Hypnotic interventions should also include direct suggestions of analgesia and delivered to a high/medium hypnotic suggestibility target population to be most

effective. As high/medium hypnotic suggestibility represents the majority of the population, this suggests treatment may be widely effective. Although the extent to which hypnotic suggestibility moderates treatment efficacy for clinical outcomes has yet to be firmly established (Montgomery et al., 2011), brief suggestibility screening (e.g., Morgan and Hilgard, 1978) may help identify therapeutic targets likely to demonstrate optimal benefits from hypnosis. In addition, some evidence indicates hypnotic suggestibility can be increased through training and practice (Patterson and Jensen, 2003), non-invasive brain stimulation (Dienes and Hutton, 2013; Coltheart et al., 2018), and pharmacological agents (Whalley and Brooks, 2009), and general engagement improved with the use of virtual reality formats (Thompson et al., 2011), which may help increase efficacy in those with low suggestibility.

4.4 Mechanisms

Although the precise analgesic mechanisms underpinning hypnosis have yet to be established, several explanations have been considered. Imaging studies reliably show hypnoanalgesic suggestion to alter activity in the anterior cingulate cortex, insular and prefrontal areas (Del Casale et al., 2015), possibly reflecting the role of these brain regions in mental relaxation, absorption and stimuli-awareness. As these areas also form a critical part of the pain neuromatrix, which plays an important part in pain modulation (Jensen and Patterson, 2014), this could provide a neural basis for hypnotic analgesia. The anterior cingulate and frontal regions may also differ across low and high suggestibles in both their structural properties and their activation in response to hypnotic induction (Jensen et al., 2017), which could account for the differential effectiveness of hypnosis across these groups.

Psychological models suggest that hypnotic induction produces an attentional shift away from external perceptual information which decreases monitoring of sensory cues and thus reduces pain (Jensen and Patterson, 2014). The fact that analgesia appears to be far more pronounced in those with high suggestibility is perhaps unsurprising, given that a greater responsivity to or willingness to engage with the

psychological components of an intervention would seem likely to enhance any therapeutic effects.

4.5 Limitations

The current findings have several important limitations. First, although evoked-pain models allow precise experimental control, chronic pain is often more sustained, diffuse and distressing, and this may threaten generalisability of the current findings to clinical pain (Arendt-Nielsen and Hoeck, 2011). Nevertheless, evidence from the current findings of meaningful pain reduction suggest a promising foundation for hypnosis as a clinical pain management technique. Second, relatively brief, one-off pain inductions were typically used, and the efficacy of hypnosis may decrease (or increase) over longer time periods. Third, reduced self-reported pain ratings might be partly attributable to undetected biases such as demand characteristics and response expectancies (Lynn et al., 2008). This concern may be partly mitigated by the analgesic effects of hypnosis for behavioural (threshold/tolerance) measures found here, and on 'objective' biomarkers such as altered brain activity in the pain matrix (Del Casale et al., 2015) and reduced medication requests in clinical settings (Lang et al., 2000; Montgomery et al., 2007) in previous studies. Fourth, the low mean study age (M=24.5, SD=4.4) questions applicability of findings to older populations where non-pharmacological interventions have the potential to be most useful due to increased sensitivity to the adverse effects of medication (Thompson et al., 2017c). Finally, we are unable to comment on the relative efficacy of hypnosis compared to analgesic medication, and there appear to be few, if any, primary studies that have directly compared the two.

4.6 Future studies

Additional well-controlled research establishing whether the current findings generalise to clinical pain is critical for establishing the viability of hypnosis as an effective pain intervention. Although the role of hypnotic intervention in clinical pain settings is well researched, limited high quality data with numerous design biases prohibits reliable conclusions (Bernardy et al., 2011; Birnie et al., 2014; Landolt and

Milling, 2011) and further well-controlled clinical studies are needed. In addition, the use of experimental models that produce hyperalgesic states (e.g. through capsaicin inflammation) and that mimic key pathological features of central sensitization in chronic pain but with strict experimental control (Chizh, 2007) are also likely to provide valuable insights.

4.7 Conclusions

This is the largest meta-analysis to date investigating the effectiveness of hypnosis as a technique for pain reduction. Evidence from 85 controlled studies provides convincing evidence that hypnosis produces substantive analgesia, with optimal pain relief delivered when direct analgesic suggestions are used in a target population of individuals high in suggestibility. Overall, the findings that hypnotic induction resulted in a reliable decrease in experimentally-induced pain suggest that hypnosis may represent a potentially effective and safe alternative or adjunct to pharmacological intervention for acute pain. Well-controlled studies of non-laboratory pain are, however, essential to establish the efficacy of hypnosis for the treatment and management of clinical pain.

5 ACKNOWLEDGEMENTS

We are very grateful to Drs Casiglia, Croft, Facco, Milling, Santarcangelo and Sandrini for their helpful responses to data requests.

6 FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

LIST OF FIGURE CAPTIONS

Figure 1. PRISMA flowchart of study selection process.

Figure 2. Forest plot of Standardised Mean Differences (with 95% confidence intervals) and study weights for 64 pain intensity studies.

Figure 3. Funnel plot of standardized mean differences (*SMD*s) from 64 pain intensity studies (filled circles) and 7 *SMD*s potentially missing due to publication bias imputed using the trim and fill method (empty circles).

LIST OF TABLE CAPTIONS

Table 1. Summary characteristics of included studies.

Table 2. Meta-regression estimates of unstandardized (0-10) pain intensity ratings and 95% confidence intervals (CI).

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Table 1. Summary characteristics of included studies.

Study	Study Design	N Hyp	N Control	Hypnotic Induction Procedure	Delivery	Analgesic Suggestion	Control Procedure	Pain Induction	Pain Measure
Derbyshire et al, 2017	RM	15	15	Standard hypnotic instructions with relaxation and imagery including suggestions to alter pain (e.g. to imagine pain on a dial with instructions to turn the dial down)	Live	Yes, No	Nothing	Heat	Intensity
Bhatt et al, 2017	RM	14	14	Standard hypnotic procedure lasting 30 mins with relaxation and positive imagery with analgesic suggestion (e.g. 'imagine the arm being completely filled with sensation of relief')	Live	Yes	Nothing	Heat	Intensity Threshold Tolerance
Fidanza et al, 2017	RM	51	51	Standard hypnotic instructions with and without glove analgesia	NS	Yes, No	Nothing	Electric	Intensity
Casiglia et al, 2017	RM	8	8	Standard hypnotic induction with disassociation (e.g. 'the hand no longer belongs to the body')	Live	No	Nothing	Cold	Intensity Tolerance
Braboszcz et al, 2017	RM	11	11	Standard hypnotic induction with relaxation and pleasant imagery plus analgesic suggestion (e.g. 'your arm cannot feel anything')	Live through headphones	Yes	Nothing	Heat	Threshold
Wolf et al, 2016	RM	37	37	Standard hypnotic induction	Live	No	Nothing	Pressure	Intensity Threshold
De Pascalis et al, 2016	RM	51	51	Stanford Hypnotic Clinical Scale	Live	No	Nothing, but told may receive analgesic or sham cream	Cold	Affect
De Pascalis et al, 2015	RM	20	20	Stanford Hypnotic Clinical Scale	Live	Yes, No	Relaxation	Electric	Intensity Affect
Kramer et al, 2014	RM	23	23	Fixation method + recall feelings of wellbeing	Live	No	Nothing	Cold + Heat + Pressure	Threshold
Swain et al, 2014	RM	120	120	*Standard hypnotic induction	Live / DVD	No	Nothing	Cold	Intensity Tolerance
Enea et al, 2014	PPC	60	30	Stanford SHSS:C	Live	Yes	Nothing	Pressure	Intensity Affect
Valentini et al, 2013	RM	24	24	Stanford SHSS:A	Live	Yes	Nothing	Heat	Intensity Affect

Santarcangelo et al, 2013	RM	40	40	Standard hypnotic induction with relaxation and pleasant imagery, plus glove analgesic suggestion (e.g. 'you cannot feel pain because the glove you are wearing prevents you from feeling it')	Live	Yes	Nothing	Cold	Intensity Threshold
Goodin et al, 2012	PPC	12	12	Modified verbal, movement and eye fixation method + glove analgesia	Live	Yes	Nothing	Cold	Intensity Affect Tolerance
Facco et al, 2011	RM	31	31	Hypnosis with relaxation and well-being suggestions	Live	Yes	Nothing	Electric	Threshold
Milling et al, 2010b	RM	173	173	Hypnosis as per Spanos (1977)	Live	Yes	Nothing	Pressure	Intensity
Milling et al, 2010a (2 experiments)	PPC	52 143	52 143	Standard hypnotic induction + glove analgesic suggestion + relaxation	Live	Yes	Nothing	Pressure	Intensity
Green et al, 2010	BG	26	24	Stanford Hypnotic Clinical Scale + glove analgesic suggestion	Live	Yes	Nothing	Ischemic	Intensity
Williams et al, 2010	RM	33	33	Standard hypnotic induction	Live	Yes, No	Not reported	Electric	Intensity
Milling et al, 2009	PPC	46	83	CURSS hypnotic induction with & without 45-sec glove analgesic suggestion	Live	Yes, No	Placebo- sham oil labelled Trivaricaine Nothing	Pressure	Intensity
Vanhaudenhuyse et al, 2009	RM	13	13	Relaxation, fixation + memory recall	Live	No	Nothing	Laser	Intensity
De Pascalis, 2008	RM	36	36	Stanford SHSS:C	Live	Yes, No	Nothing	Electric	Intensity Affect
Roder et al, 2007	RM	7	7	Hypnosis + Fixation + relaxation Hypnosis +Fixation + depersonalization	Live	No	Nothing	Electric	Intensity
Casgalia et al, 2007	RM	20	20	Hypnosis with suggestion of relaxation and analgesia	Live	Yes	Nothing	Cold	Intensity Tolerance
Milling et al, 2007	PPC	42	41	CURSS	Live	Yes	Placebo- sham oil labelled Trivaricaine Nothing	Pressure	Intensity
Sharav et al, 2006	RM	25	25	Hypnotic induction with generalized relaxation, guided imagery and focused analgesia	Live	Yes	Nothing	Electric	Intensity
Patterson et al, 2006	PPC	51	26	Stanford Hypnotic Clinical Scale with relaxation + analgesic/no analgesic suggestion	Audio recording	Yes, No	Nothing	Heat	Intensity Affect
Milling et al, 2005	RM	40	40	CURSS + glove analgesic suggestion	Live	Yes	Placebo topical oil Nothing	Pressure	Intensity

Rainville et al, 2005	RM	69	69	Standard hypnotic induction	Live	No	Nothing	Heat	Intensity Affect
De Pascalis, Cacace et al, 2004	RM	38	38	Stanford SHSS:C	Live	Yes, No	Nothing	Electric	Intensity Affect
De Pascalis, Bellusci et al, 2004	RM	30	30	Stanford SHSS:C with relaxation + dissociation	Live	Yes, No	Placebo	Cold	Intensity
Sharav et al, 2004	RM	15	15	Hypnotic relaxation induction with/without focused analgesic suggestion	Live	Yes, No	Nothing	Electric	Intensity
Milling and Breen, 2003	PPC	55	55	CURSS with pain control or glove analgesic suggestion	Audio recording	Yes, No	Placebo- sham oil labelled Trivaricaine Nothing	Pressure	Intensity
Milling, Levine et al, 2003	PPC	95	47	CURSS	Live	Yes, No	Nothing	Pressure	Intensity
Faymonville et al, 2003	RM	19	19	Hypnosis with eye fixation and muscle relaxation	Live	Yes	Nothing	Heat	Intensity
Croft et al, 2002	BG	11	9	Hypnosis with relaxation, fixation and imagery	Live	Yes, No	Oddball task	Electric	Intensity
Milling et al, 2002	PPC	22	18	CURSS + glove analgesia	Live	Yes	Nothing	Pressure	Intensity
Langlade et al, 2002	RM	15	15	Hypnosis with fixation, relaxation and analgesic suggestion	Live	Yes	Nothing	Heat	Threshold Tolerance
Ray et al, 2002	RM	12	12	Stanford SHSS:C	Audio recording	Yes	Nothing	Electric	Intensity
Friederich et al, 2001	RM	20	20	Stanford Hypnotic Clinical Scale glove analgesic suggestion + relaxation imagery	Live	Yes	Nothing	Heat	Intensity Affect
Wright et al, 2001	PPC	30	28	Rapid induction Analgesia	Live	Yes	Reading	Chemical Pressure	Intensity Affect Threshold Tolerance
De Pascalis et al, 2001	RM	29	29	Stanford SHSS:C with relaxation, dissociation and analgesic suggestion	Live	Yes, No	Nothing Placebo topical anaesthetic	Electric	Intensity Affect
Benhaiem et al, 2001	RM	32	32	Hypnosis with deep relaxation and focused analgesia	Live	Yes, No	Nothing	Heat	Threshold

Hofbauer et al, 2001	RM	10	10	Stanford SHSS:A	Live	Yes, No	Nothing	Heat	Intensity Affect
Faymonville et al, 2000	RM	11	11	Stanford SHSS:C with muscle relaxation and pleasant memory recall	Live	No	Nothing	Heat	Intensity Affect
Sandrini et al, 2000	RM	20	20	Standard hypnotic induction	Live	Yes	Nothing	Cold	Tolerance
De Pascalis et al, 1999	RM	29	29	Stanford SHSS:C with relaxation, dissociative imagery and analgesic suggestion	Live	Yes, No	Nothing Placebo topical gel	Electric	Intensity Affect Threshold
Rainville et al, 1999	PPC	11	6	Stanford SHSS:A	Live	Yes	Nothing	Heat	Intensity Affect
Milling et al, 1999	PPC	50	48	Stanford SHSS:C	Audio recording	Yes	Nothing	Pressure	Intensity
Danziger et al, 1998	RM	18	18	Hypnosis with deep relaxation, fixation and Analgesic suggestion	Live	Yes	Nothing	Electric	Threshold
Zachariae et al, 1998	RM	20	20	Standard hypnotic induction	Live	Yes, No	Nothing	Electric	Intensity
Rainville et al, 1997	RM	8	8	Stanford SHSS:A	Live	Yes, No	Nothing	Heat	Intensity Affect
De Pascalis et al, 1997	RM	20	20	Stanford SHSS:C with subjective sensitivity to somatosensory stimuli emphasised	Audio recording	Yes, No	'normal attention' control (recognition task)	Electric	Intensity Threshold
De Pascalis et al, 1996	RM	16	16	Stanford SHSS:C	Live	Yes, No	Nothing	Electric	Intensity Affect
Jacobs et al, 1995	RM	24	24	Stanford SHSS:C	Audio recording	Yes	Nothing	Cold	Intensity
Kiernan et al, 1995	RM	15	15	Hypnosis with suggestion of relaxation, comfort, and wellbeing	Live	Yes	Nothing	Electric	Intensity Affect
Hargadon et al, 1995	RM	66	66	Standard hypnotic induction with glove analgesic suggestion	Live	Yes	Nothing	Pressure	Intensity
Dahlgren et al, 1995	RM	16	16	Stanford hypnotic clinical scale with deep relaxation	Live	Yes	Nothing	Cold	Intensity Affect
Zachariae et al, 1994	RM	20	20	Hypnosis using eye fixation technique and standardised countdown deepening procedure with deep relaxation/ dissociative imagery/ focused analgesia	Live	Yes, No	Placebo anaesthetic spray	Laser	Intensity

Crawford et al, 1993	RM	11	11	Stanford SHSS:C with mention of sleep and drowsiness	NG	Yes, No	Nothing	Ischemic	Intensity Affect
Maurer et al, 1993	RM	42	42	Direct hypnosis induction with focused attention and repetitive direct suggestion Indirect hypnosis with 'Rapid Induction Analgesia'	Live	Yes	Nothing	Cold	Intensity
Spanos et al, 1990 (2 experiments)	PPC (RM)	15 28	15 28	Hypnosis (Barber, 1969)	Audio recording	Yes	Nothing	Pressure	Intensity
Tenenbaum et al, 1990	RM	48	48	Stanford Hypnotic Clinical Scale	Audio recording	Yes	Nothing	Cold	Tolerance
Malone et al, 1989	RM	45	45	Hypnosis (Barber, 1969) with relaxation and analgesic suggestion	Live	Yes, No	Nothing	Electric	Intensity Affect
Spanos, Perlini et al, 1989 2 experiments	PPC	64 60	32 30	Hypnosis (Barber, 1969)	Live	Yes	Nothing	Pressure	Intensity
Spanos and Katsanis, 1989	PPC	20	10	Hypnosis modified from Barber (1969) as passively (analgesia without voluntary effort) or actively (analgesia due to mental control) worded instructions	Live	Yes	Nothing	Pressure	Intensity
De Benedettis et al, 1989	RM	21	21	Standard hypnotic induction	Live	Yes`	Nothing	Ischemic	Affect Tolerance
Spanos et al, 1988	PPC	45	15	Hypnosis (Barber, 1969)	Live	Yes	Nothing	Pressure	Tolerance
Price et al, 1987	RM	16	16	Standard hypnotic induction	Live	Yes	Nothing	Heat	Intensity Affect
Stam et al, 1987	RM	32	32	Standard hypnotic Induction	Live	Yes	Nothing	Ischemic	Threshold Tolerance
Spanos et al, 1986	PPC	64	32	Hypnosis (Barber, 1969)	Audio recording	Yes	Nothing	Pressure	Intensity Tolerance
Van Gorp et al, 1985	PPC	20	20	Rapid induction analgesia which includes suggestion of relaxation and altering memory Standard hypnotic induction	Audio recording	Yes, No	Nothing	Cold	Intensity
Spanos et al, 1985	PPC	21	19	Hypnosis (Barber, 1969)	Audio recording	Yes	Nothing	Cold	Tolerance

Fricton et al, 1985	RM	10	10	Indirect hypnosis induction uses language that is individualised – implies control rests with the subject Direct hypnosis induction uses focused attention and repetitive direct suggestion	Live	No	Nothing	Electric	Threshold
Spanos et al, 1984	RM	75	75	Hypnosis (Barber, 1969)	Live	Yes	Nothing	Cold	Intensity
Stam et al, 1984 (2 experiments)	RM (PPC)	16 10	16 10	Standard hypnotic induction	Audio recording	Yes	Nothing	Ischemic	Threshold Tolerance
Spanos et al, 1983	RM	16	16	Hypnosis (Barber, 1969) with suggestions of more or less aware of pain from overt and hidden part of body	Audio recording	Yes	Nothing	Cold	Intensity
Karlin et al, 1980	RM	11	11	Standard hypnotic induction	Audio recording	Yes	Nothing	Cold	Intensity
Spanos et al, 1980	RM	8	8	Hypnotic induction with hidden observer cues	Audio recording	Yes	Nothing	Cold	Intensity
Stam et al, 1980	PPC	20	10	Standard hypnotic procedure	Live	Yes	Nothing	Cold	Intensity
Wood et al, 1976	PPC	10	10	Standard hypnotic induction	Audio recording	No	Nothing	Cold	Tolerance
Lli et al, 1975	RM	14	14	Standard hypnotic induction with relaxation	Live	Yes	Nothing	Electric	Tolerance Threshold
Greene et al, 1972	RM	36	36	Standard hypnotic induction with pleasant imager with/without analgesic suggestion	Live	Yes, No	Nothing	Electric	Tolerance
Morgan et al, 1970	RM	12	12	Standard hypnotic induction	NG	Yes	Nothing	Cold	Intensity
Evans et al, 1970	PPC	32	16	Hypnotic induction with eye fixation & relaxation	Live	Yes, No	Nothing	Cold	Affect

Key. RM=repeated-measures; BG=between-groups; PPC=pre-post control; CURSS=Carlton University Responsiveness to Suggestion Scale; SHSS=Stanford Hypnotic Suggestibility Scale (Forms A and C).

Table 2. Meta-regression estimates of unstandardized (0-10) pain intensity ratings and 95% confidence intervals (CI).

	Estimate	95% CI	p
Intercept	0.03	-0.59, 0.64	.931
Hypnotisability (Medium)	0.64	0.26, 1.03	.003
Hypnotisability (High)	1.34	0.75, 1.93	<.001
Analgesic suggestion (Yes)	0.94	0.25, 1.63	.009

Figure 1. PRISMA flow diagram

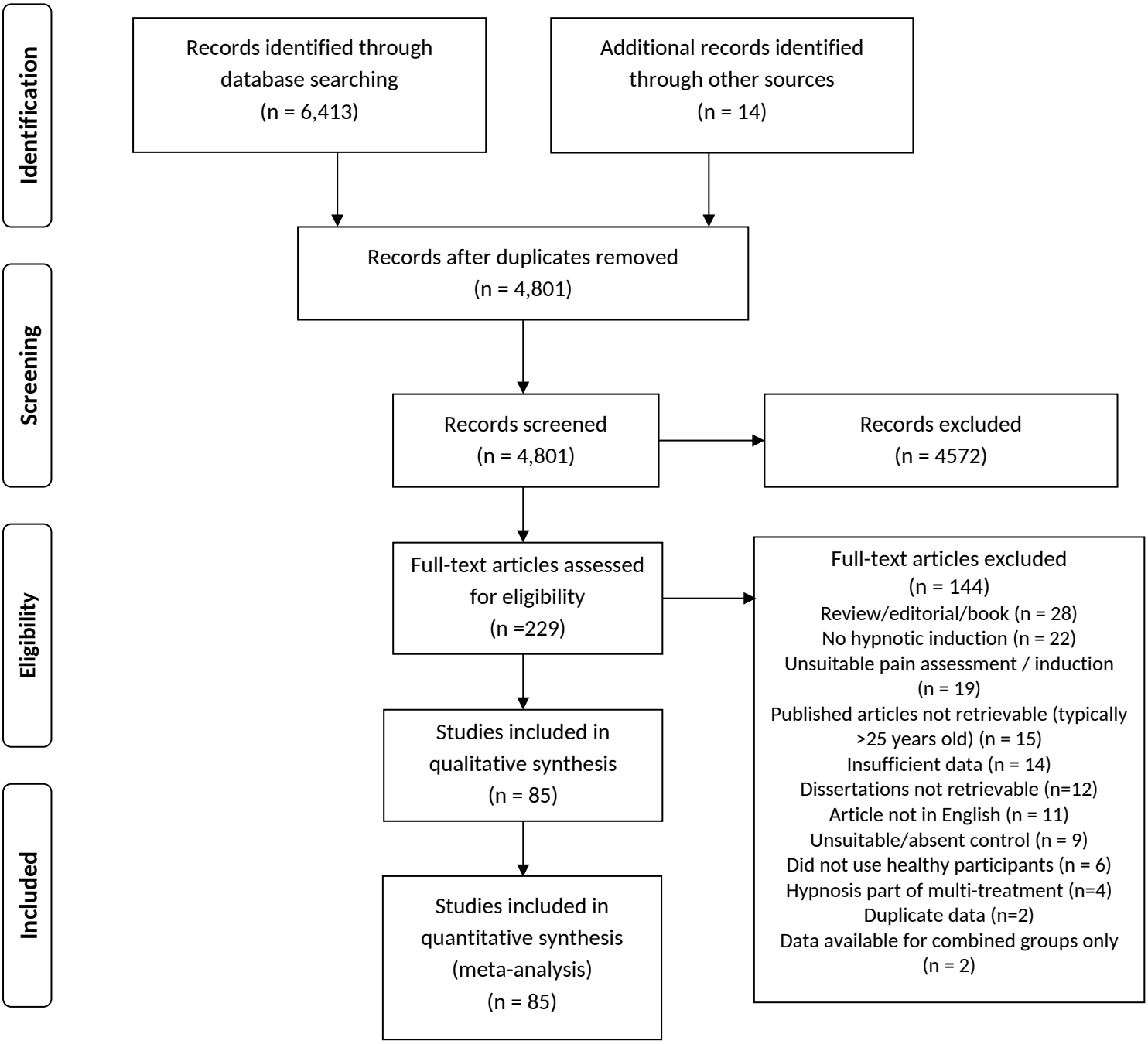
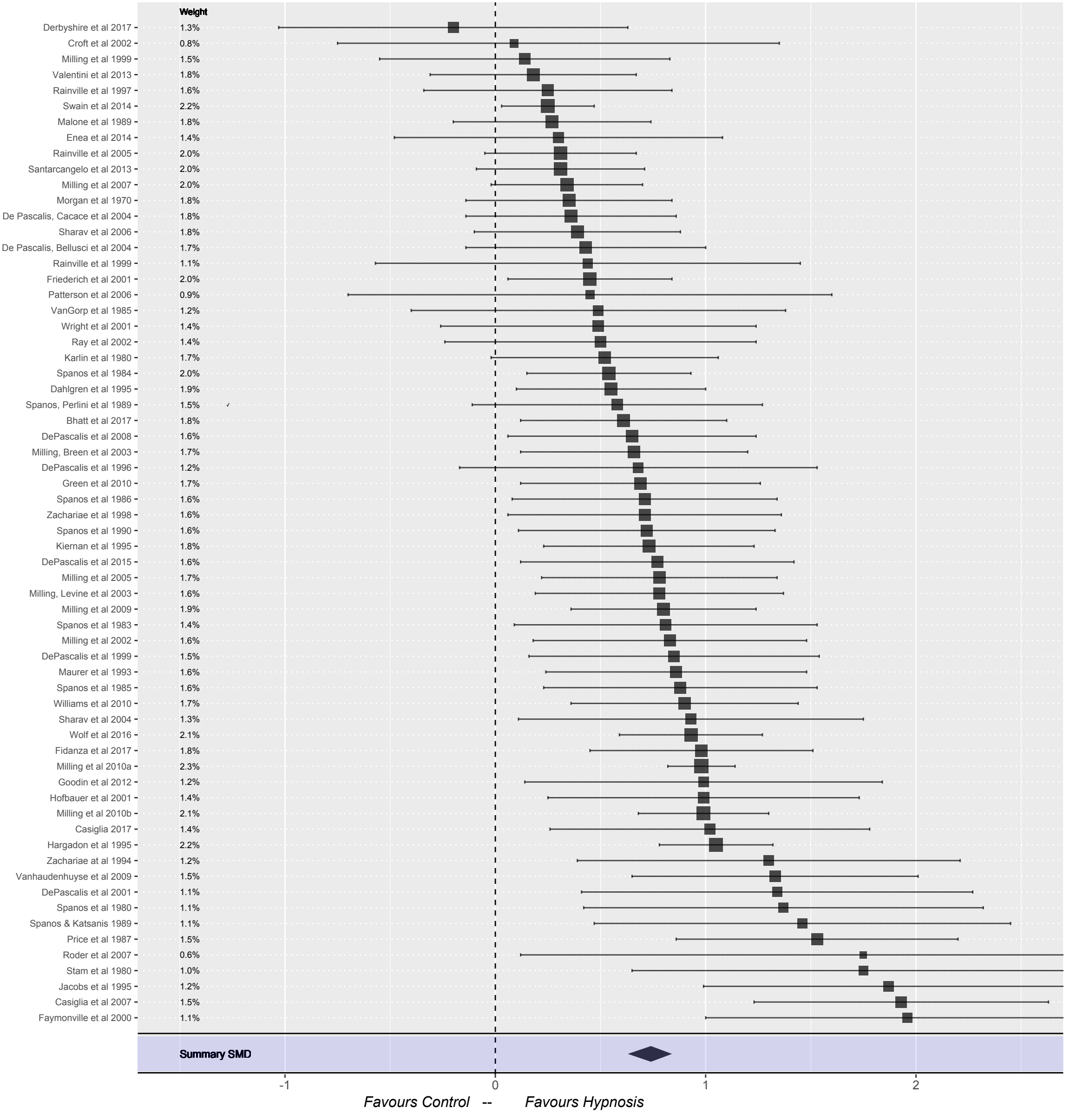
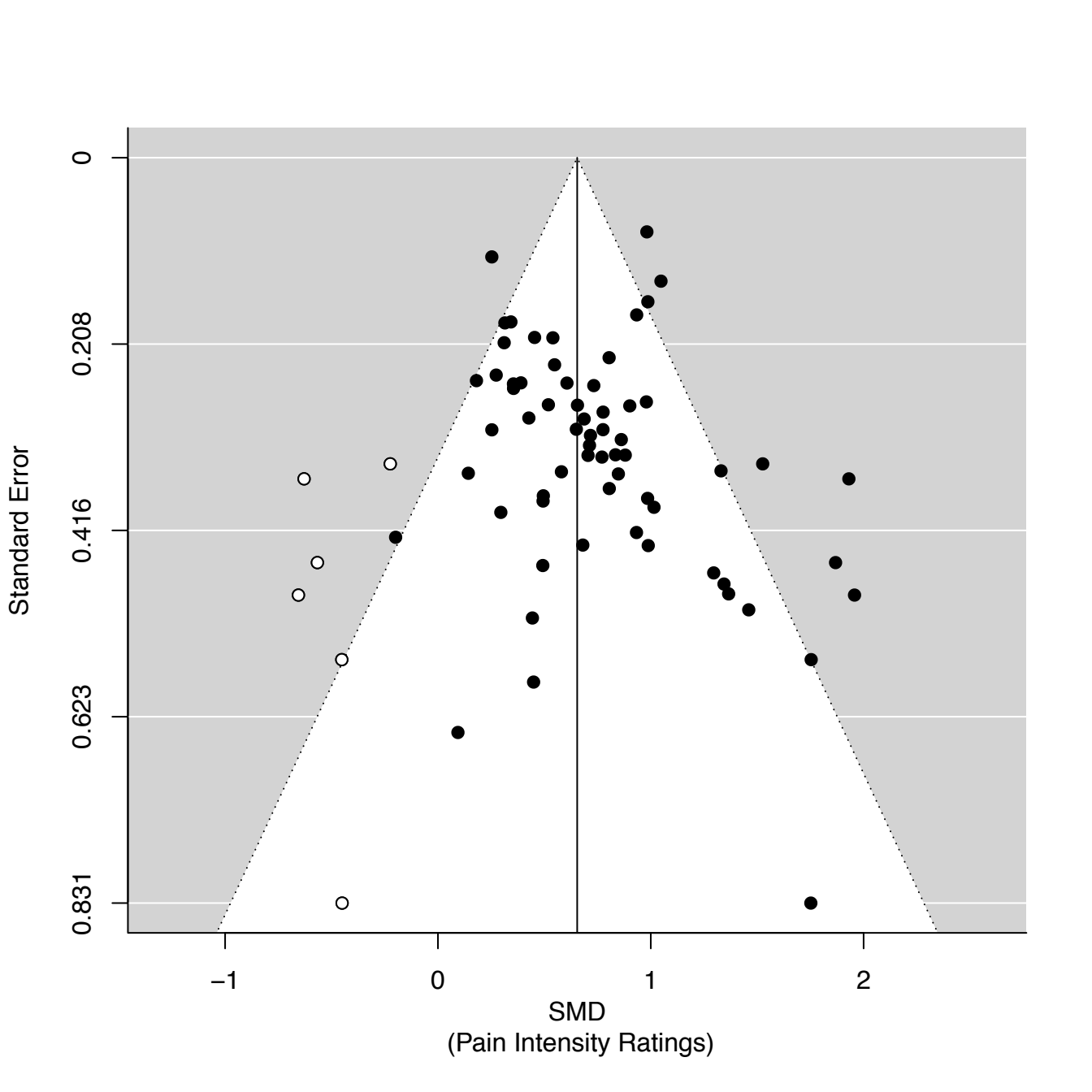


Figure 2. Forest plot of pain intensity




Standard Error
0
0.208
0.416
0.623
0.831
−1
0
1
2
SMD
(Pain Intensity Ratings)

Appendix S1. Search terms for PubMed

(hypno* OR trance) AND (pain OR nocicept* OR analge*) AND (threshold OR tolerance OR cold OR heat OR thermal OR ischemi* OR ischaemi* OR chemical OR pressure OR mechanical OR electric* OR chemical OR capsaicin OR reflex OR experimental OR acute)

Appendix S2. Endorsement of validity criteria (1= criteria met, 0= criteria not met)

Study	q1	q2	q3	q4	q5	q6	q7	q8	q9	q10	q11	q12	q13	q14	q15
Derbyshire et al (2017)	1	1	1	0	0	0	1	1	1	0	1	1	1	1	1
Bhatt et al (2017)	1	1	0	1	1	0	1	1	1	1	0	1	1	1	0
Fidanza et al (2017)	1	1	0	1	0	1	1	1	0	0	1	1	1	1	0
Casiglia et al (2017)	1	0	0	0	0	0	1	1	0	0	0	1	0	1	0
Braboszcz et al (2017)	1	1	1	0	0	0	0	1	1	1	1	1	1	1	1
Wolf et al (2016)	1	1	1	1	0	1	0	1	1	0	0	1	0	1	1
DePascalis et al (2016)	1	1	1	1	1	1	1	1	0	1	1	1	1	1	0
DePascalis et al (2015)	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1
Kramer et al (2014)	1	0	1	1	0	0	1	1	1	0	1	1	1	1	0
Swain et al (2014)	1	1	1	1	1	0	1	1	0	1	0	0	1	1	0
Enea et al (2014)	1	1	1	0	0	0	1	1	1	1	1	1	0	1	1
Valentini et al (2013)	1	0	0	1	1	1	1	1	1	0	1	1	1	1	1
Santarcangelo et al (2013)	1	1	1	1	1	0	1	1	0	1	1	1	1	1	0
Goodin et al (2012)	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1
Facco et al (2011)	1	1	0	1	1	1	1	1	1	0	1	1	1	1	0
Williams et al (2012)	1	0	0	0	0	0	1	1	0	0	1	1	1	1	1
Milling et al (2010)	1	1	1	0	0	0	1	0	0	1	1	1	1	1	0
Green et al (2010)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
Milling et al (2010)	1	1	1	1	1	0	1	1	0	1	0	0	1	1	0
Milling et al (2009)	1	1	1	0	1	0	1	1	1	1	1	0	1	1	1
Vanhaudenhuyse et al (2009)	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1
DePascalis et al (2008)	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1
Roder et al (2007)	1	0	0	0	0	0	1	1	1	0	1	0	1	1	0
Casiglia et al (2007)	1	0	0	0	0	1	1	1	1	0	0	1	1	1	0
Milling et al (2007)	1	1	1	0	0	0	1	1	1	1	1	0	1	1	1
Sharav et al (2006)	1	1	1	0	0	0	1	1	1	0	1	1	1	1	0
Patterson et al (2006)	1	1	0	0	0	0	1	1	1	0	1	0	1	1	1

Milling et al (2005)	1	1	1	0	0	0	1	1	1	1	1	0	0	1	1
Rainville et al (2005)	1	1	0	0	0	0	1	1	0	1	1	1	1	1	0
DePascalis, Cacace et al (2004)	1	1	0	0	0	0	1	1	0	1	1	1	1	1	1
DePascalis, Bellusci et al (2004)	1	1	1	1	0	0	1	1	1	0	1	1	1	1	0
Sharav et al (2004)	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0
Milling, Breen et al (2003)	1	1	1	0	0	0	1	1	1	1	1	0	0	1	1
Faymonville et al (2003)	1	0	0	0	0	0	1	1	1	1	1	1	1	1	0
Milling, Levine et al (2003)	1	1	1	0	0	0	1	1	1	0	1	0	0	1	1
Croft et al (2002)	1	1	1	0	0	0	1	1	1	0	1	0	1	1	1
Milling et al (2002)	1	1	1	0	0	0	1	1	1	1	1	1	0	1	1
Langlade et al (2002)	0	1	1	0	0	0	1	1	0	0	0	1	1	1	1
Ray et al (2002)	1	1	0	0	0	0	0	1	0	1	0	1	1	1	0
Wright et al (2001)	1	1	1	0	0	0	1	1	1	0	0	1	1	1	0
DePascalis et al (2001)	1	1	0	1	0	0	1	1	1	1	1	1	1	1	0
Benhiem et al (2001)	1	0	1	1	0	1	1	1	1	0	1	1	1	1	0
Hofbauer et al (2001)	1	0	0	0	0	0	1	1	1	1	1	1	1	1	0
Freiderich et al (2001)	1	1	1	0	0	0	1	1	1	1	1	0	0	1	1
Faymonville et al (2000)	1	0	0	0	0	1	1	1	0	0	1	1	1	1	0
Sandrini et al (2000)	1	1	0	0	0	1	1	1	1	0	1	1	1	1	1
DePascalis et al (1999)	1	0	0	0	0	0	1	1	1	1	1	1	1	1	0
Rainville et al (1999)	1	1	0	0	0	0	1	1	1	1	0	1	1	1	0
Milling et al (1999)	1	1	1	0	0	0	1	1	0	0	1	1	0	1	1
Danzinger et al (1998)	1	1	0	1	0	1	0	1	1	0	1	1	0	1	0
Zachariae et al (1998)	1	0	1	0	0	0	1	1	1	1	1	0	1	1	0
Rainville et al (1997)	1	0	0	0	0	0	0	1	0	1	1	1	0	1	0
DePascalis et al (1997)	1	1	1	0	0	0	1	1	0	0	1	1	0	1	0
DePascalis et al (1996)	1	1	0	0	0	0	1	1	0	1	1	1	1	1	0
Jacobs et al (1995)	1	1	1	0	0	0	1	1	0	0	1	1	0	1	0
Kiernan et al (1995)	1	1	1	1	0	1	1	0	1	0	0	1	1	1	0

Hargadon et al (1995)	1	0	0	0	0	0	1	1	1	1	1	1	0	1	0
Dahlgren et al (1995)	1	1	0	1	0	1	0	0	0	1	1	1	0	1	0
Zachariae et al (1994)	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1
Maurer et al (1993)	1	1	0	0	0	0	1	1	1	1	1	1	1	1	0
Crawford et al (1993)	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1
Spanos et al (1990)	1	1	1	0	0	0	1	1	1	1	1	0	0	1	1
Tenenbaum et al (1990)	1	0	1	1	0	1	1	1	0	0	1	0	0	1	0
Malone et al (1989)	0	1	1	0	0	0	1	1	1	0	1	0	0	1	1
Spanos, Perlini et al (1989)	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1
Spanos and Katsanis et al (1989)	1	1	1	0	0	0	1	1	1	1	1	0	0	1	1
Debenedittis et al (1989)	1	1	1	0	0	0	1	1	1	0	1	1	1	1	0
Spanos et al (1988)	1	1	1	0	0	0	1	1	1	1	1	0	1	1	1
Stam et al (1987)	1	1	1	1	0	1	1	1	0	1	0	1	1	1	0
Price et al (1987)	1	1	1	0	0	0	1	1	1	0	0	1	1	1	0
Spanos et al (1986)	1	1	1	0	0	0	1	1	1	1	1	1	0	1	1
VanGorp et al (1985)	1	1	0	0	0	0	1	1	1	1	1	1	0	1	1
Spanos et al (1985)	1	1	1	0	0	0	1	1	1	1	0	1	0	1	1
Fricton et al (1985)	1	0	0	0	0	0	1	1	1	0	1	1	0	1	0
Spanos et al (1984)	1	1	1	0	0	0	1	1	1	0	1	1	1	1	1
Stam et al (1984)	1	1	1	1	1	0	1	1	1	1	1	0	1	1	0
Spanos et al (1983)	1	1	1	1	0	0	1	1	1	0	1	1	0	1	0
Karlin et al (1980)	0	1	1	1	0	0	1	1	0	0	1	1	1	1	0
Stam et al (1980)	1	1	1	0	0	0	1	1	1	1	1	1	1	1	1
Spanos et al (1980)	1	1	1	0	0	0	1	1	1	1	1	1	0	1	0
Wood et al (1976)	1	1	0	0	0	0	1	1	1	1	1	0	0	1	0
Li et al (1975)	0	1	0	1	1	0	0	1	1	1	0	0	1	1	0
Greene et al (1972)	1	1	1	0	0	0	1	1	1	1	1	1	0	1	1
Morgan et al (1970)	1	0	0	0	0	0	1	1	0	0	1	1	0	1	0
Evans et al (1970)	1	1	1	0	0	0	1	1	1	0	1	0	1	1	0

Mean Item Endorsement	**0.95**	**0.79**	**0.64**	**0.34**	**0.18**	**0.25**	**0.92**	**0.96**	**0.71**	**0.59**	**0.82**	**0.73**	**0.67**	**1.00**	**0.42**

Key: 1-Was there a clear specification of study objectives; 2-Was it clearly described where particpants were drawn from (e.g. University etc); 3-Was it clearly described how participants were recruited (e.g. advertisement, course credits, volunteers etc etc); 4-Was there a clear description of the inclusion and exclusion criteria; 5-Were participants assessed to see if they had pre-existing pain; 6-Were participants asked to report (or abstain from using) any medication that might affect their experience of pain (e.g. painkilllers); 7-Pain Assessment: Was the method of pain assessment clearly described; 8-Pain Induction: Was the method of pain induction clearly reported; 9-Hypnosis: Was the hypnotic intervention described in adequate detail; 10-Control: Was the control condition described in adequate detail; 11-Was hypnotisability assessed; 12-Comparability of cases and controls; 13-Were relevant participant characteristics adequately described (age, sex etc); 14-Were complete outcome data (i.e., Ms and SDs) available (e.g. reported in article or given via response to data request); 15-Were paticipants randomly allocated to groups (independent-sample designs) or presentation order (repeated-measures designs)?

PRISMA 2009 Checklist

`Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Table S1
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, Fgiure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12, Table S1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	14-15
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17, 19
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	20

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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