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PII: S1568-1637(16)30305-1
DOI: http://dx.doi.org/doi:10.1016/j.arr.2017.01.005
Reference: ARR 741

To appear in: *Ageing Research Reviews*

Received date: 19-12-2016
Revised date: 25-1-2017
Accepted date: 25-1-2017

Please cite this article as: Thompson, Trevor, Gallop, Katy, Correll, Christoph U., Carvalho, Andre F., Veronese, Nicola, Wright, Ellen, Stubbs, Brendon, Pain perception in Parkinson's disease: A systematic review and meta-analysis of experimental studies.Ageing Research Reviews http://dx.doi.org/10.1016/j.arr.2017.01.005

Pain perception in Parkinson's disease: A systematic review and meta-analysis of experimental studies

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Number of pages: 31
Number of figures: 2
Number of tables: 1
Online appendices: 1
Word count (exc. abstract, references, appendix, tables): 5469

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Highlights

Meta-analysis of pain studies comparing parkinsons disease (PD) vs. healthy controls

PD patients demonstrate hypersensitivity to pain (hyperalgesia)

Hyperalgesia greatest during unmedicated OFF states

Evidence supports dopamine deficiency as an underlying mechanism

Hyperalgesia could contribute to onset/intensity of clinical pain in PD

Disclosures

TT, KG, NV, EW and BS have no conflicts of interest. AFC is supported by a research fellowship award from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; Brazil). CUC has been a consultant and/or advisor to or has received honoraria from: Alkermes, Allergan, Bristol-Myers Squibb, Forum, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, Medavante, Medscape, Neurocrine, Otsuka, Pfizer, ProPhase, Sunovion, Supernus, Takeda, and Teva. He has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka. He served on a Data Safety Monitoring Board for Lundbeck and Pfizer. He received grant support from Takeda.

Abstract

While hyperalgesia (increased pain sensitivity) has been suggested to contribute to the increased prevalence of clinical pain in Parkinson's disease (PD), experimental research is equivocal and mechanisms are poorly understood. We conducted a meta-analysis of studies comparing PD patients to healthy controls (HCs) in their response to experimental pain stimuli. Articles were acquired through systematic searches of major databases from inception until 10/2016. Twenty-six studies met inclusion criteria, comprising 1,292 participants (PD=739, HCs=553). Random effects meta-analysis of standardized mean differences (*SMD*) revealed lower pain threshold (indicating hyperalgesia) in PD patients during unmedicated OFF states (*SMD*=0.51) which was attenuated during dopamine-medicated ON states (*SMD*=0.23), but unaffected by age, PD duration or PD severity. Analysis of 6 studies employing suprathreshold stimulation paradigms indicated greater pain in PD patients, just failing to reach significance (*SMD*=0.30, *p*=.06). These findings (a) support the existence of hyperalgesia in PD, which could contribute to the onset/intensity of clinical pain, and (b) implicate dopamine deficiency as a potential underlying mechanism, which may present opportunities for the development of novel analgesic strategies.

Keywords: Parkinson's disease, dopamine, pain, meta-analysis, systematic review.

1 Introduction

Chronic pain is a common non-motor symptom of Parkinson's disease (PD). A recent systematic review indicated a mean pain prevalence of 68% in PD patients [6], with another study finding that chronic pain complaints, especially musculoskeletal pain, were twice as likely and reported as twice as intense in PD patients compared to age-matched controls with other chronic disorders [42]. Pain often appears early in the development of PD and may be present years before clinical diagnosis [49]. Pain has been rated as the most burdensome non-motor symptom [7], and contributes to PD-related disability, sleep disturbance, and impaired quality of life [9, 19, 46]. Non-motor symptoms including pain are also a frequent cause of hospitalisation and institutionalisation of PD patients and can increase healthcare costs by up to four times [9]. Nevertheless, pain is a frequently overlooked symptom of PD, often unreported by patients unaware that painful symptoms are linked to the disease [36], and consequently under-treated [6] which can increase the overall burden of PD. This is especially unfortunate given that pain represents a non-motor symptom that is eminently treatable [8].

While pain in PD is often precipitated by muscular rigidity and/or postural abnormalities [22], neurodegenerative processes could potentially affect not only motor function, but also peripheral [43] and brain [19] pathways involved in pain processing. For example, degradation of dopamine-producing cells in the substantia nigra may impair natural analgesia by disrupting the dopamine-mediated descending pathways that block transmission of ascending nociceptive signals from the spinal cord [19]. A role of dopamine in pain is consistent with reduced pain sensitivity seen in schizophrenia [53], a disorder linked to dopamine dysregulation, and the possible partial restoration of normal pain thresholds in PD during functional ON states following treatment with dopaminergic agents [13].

If pain processing is affected centrally in PD, as hypothesised, this could result in a generalised hypersensitivity to noxious sensations [13], which may influence the onset of and/or exacerbate painful symptoms in PD [6]. Evidence for this hypersensitivity is, however, inconsistent. While several studies have found increased pain sensitivity in PD patients compared to healthy controls (HCs) in response to noxious experimental stimulation [10, 32, 39], others have failed to find such an effect [25, 35, 61]. This inconsistency may be influenced by methodological differences across studies, including variation in sample size, dopaminergic and analgesic medications, disease duration and symptom severity [19, 45]. Nevertheless, to our knowledge, there has been no systematic effort to synthesize available evidence from experimental studies and to explore potential sources of study heterogeneity using meta-analytic techniques. Examining the influence of dopamine medication may be especially revealing, both to provide evidence for possible mechanisms of action and for informing potential analgesic treatment.

We therefore conducted a systematic review and meta-analysis of studies comparing PD patients and HCs in their response to noxious experimental stimuli to: (1) examine whether PD patients and HCs differ in their response to experimentally-induced pain; (2) quantify the magnitude of this difference; and (3) explore potential moderators of this association including dopaminergic agents, disease duration, and symptom severity.

2 Method

This systematic review and meta-analysis was conducted in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement [37] and the

Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [52] for observational studies. An *a priori* established but unpublished protocol was followed.

2.1 Eligibility criteria

The following inclusion criteria were applied: (1) use of a group with primary (idiopathic) Parkinson's disease (PD), based on standardized diagnostic criteria (e.g. UK Brain Bank); (2) inclusion of a comparative healthy control (HC) group without PD; (3) application of an experimental pain stimulus; and (4) a quantitative assessment of pain. We excluded studies using participants with secondary Parkinsonism only (e.g. from toxin exposure) and those published in languages other than English.

2.2 Search strategy

EMBASE, MEDLINE and PsycINFO databases were independently searched by two reviewers (KG, TT) with the final search performed on 10th October, 2016. The following search terms were used: (Parkinson's disease(MeSH) OR Parkinson's) AND (pain(MeSH) OR pain OR nociception) to identify the largest possible pool of potentially eligible studies. The search results were *a posteriori* refined using limits of 'human studies' and 'English language'. This search strategy was augmented through hand searching reference lists of included articles and relevant reviews.

2.3 Study selection

After removal of duplicates, two reviewers (KG, TT) independently screened titles/abstracts for eligibility, and resolved disagreements through consensus. The full-text of potentially eligible articles was then independently scrutinized by two authors (TT, BS). Following consensus, a full-list of eligible articles was defined. When a study provided insufficient data

for inclusion, corresponding authors were contacted up to 3 times over an 8-week period to request additional data. Of 8 author groups contacted, 6 [3, 25, 28, 41, 43, 54] provided data sufficient to permit study inclusion.

2.4 Pain outcome variables

The following pain outcomes were used: (1) pain threshold (the point at which pain is first reported), (2) pain tolerance (the point at which pain is reported as no longer tolerable), and (3) self-report ratings of pain intensity/affect. We used these multiple outcomes to assess whether different aspects of the pain experience were selectively affected in PD. Threshold involves low-intensity pain and is influenced primarily by sensory processes (e.g., localization and initial detection), whereas tolerance is a suprathreshold measure more strongly influenced by affective mechanisms [2]. Pain rating scales provide an easily interpretable index of subjective pain and typically assess sensory (e.g., intensity) or affective (e.g., discomfort) dimensions of pain on a VAS or numerical rating scale.

Sensory threshold (the point at which sensation is first reported) was included as a secondary measure to examine whether PD was also associated with non-painful sensory impairment. As we only wished to examine direct measures of pain, we did not examine supplementary physiological data.

2.5 Data Extraction

Extraction and coding of study data was performed by two authors (TT, KG), on a standardized form adapted from our previous studies [53, 57]. The following data were extracted where available: (1) sociodemographic variables; (2) For PD groups: mean disease duration (years), symptom severity score, functional state (ON/OFF), body side tested

(least/most affected), diagnostic criteria used, cognitive impairment, usual treatment, % of sample with PD-based clinical pain; (3) pain outcomes and pain induction method. Means and standard deviations for each pain outcome were recorded, and any other available information that allowed effect size computation [33]. To reduce reporting bias, authors were contacted for statistical details when findings were simply reported as 'non-significant'.

A number of decisions were made when computing effect sizes from extracted data. First, a few studies (*k*=3) provided data from multiple independent participant samples [3, 48, 61], e.g. with/without dyskinesia, and were treated as separate studies in the analysis [4]. Second, for one study that used a wide range of temperatures [41], only those eliciting a self-report of pain (47.5˚C and 49.5˚C) were included. Third, for studies (*k*=2) that reported the use of different noxious electrical frequencies [3, 10], the lowest frequency was arbitrarily selected, as there appears to be no persuasive evidence for a frequency effect [10]. Fourth, where studies performed repeated pain assessments on the same set of participants (e.g. across different stimuli), multiple effect sizes were computed for each assessment with any dependency across effect sizes modeled using robust variance estimation (RVE) (see Section 2.7.2).

2.6 Study validity criteria

Two authors (KG, TT) independently rated each study on several dichotomous validity criteria, with a third author (BS) available for mediation in the event of disagreement. We assessed case/control comparability and participant selection with 5 items from the Newcastle Ottawa Scale [62], and methodological soundness with 14 items based on Cochrane Collaboration principles as reviewed by Deeks at al. [14] (see Table 1). Overall

scores were not computed due to concerns over their interpretability [14], but the impact of poorly endorsed validity criteria was examined in moderator analysis.

2.7 Statistical analysis

2.7.1 *Effect size*

A standardized mean difference (*SMD*) for PD vs. control groups was computed for each study using Hedges' *g* formula [4]. Hedges' *g* is equivalent to Cohen's *d*, but corrects for bias in small samples. Effect sizes can be interpreted as .20,.50 and.80 corresponding to small, medium and large effects respectively [12].

Effect size (ES) was coded so that positive values indicated higher pain in the PD compared to the HC group.

2.7.2 *Meta-analysis*

An overall summary effect size for each outcome was estimated using random-effects meta-analysis. A random-effects model was chosen as heterogeneity was expected based on similar meta-analyses conducted for other disease conditions [53, 57]. Several studies reported multiple ES data from the same samples and a few studies used different PD sample but with the same control group comparisons. Conventional meta-analytic techniques that assume independence of effect sizes were therefore not considered appropriate. Instead, we used a robust variance estimation (RVE) method [29], which adjusts individual ES weights based on the degree of their dependency. We employed a relatively new version of RVE for correlated effect sizes, which provides reliable estimates even when relatively low numbers of studies are available. Simulation studies have demonstrated accurate estimation, provided that the adjusted RVE *degrees of freedom* (*df)* > 4 [58], and

this criterion is used here (*df* is larger when study number is high and when multiple effect sizes from a study are relatively independent). RVE estimates dependency from the data itself, and therefore is a superior approach to averaging across conditions, which results in both information loss and relies on a knowledge of the correlations of outcomes across conditions which are rarely reported [20].

Separate analyses were conducted for OFF/ON functional states, to examine whether pain sensitivity is altered by treatment (typically dopaminergic medication). For the specific outcome of pain ratings, we only examined *k*=5 out of 7 studies where stimulation intensity was identical for both the PD and control groups (i.e., where a fixed-intensity/fixed-time paradigm was used), to avoid any confounding of group differences in pain ratings with group differences in stimulation intensity.

2.7.3 *Meta-regression analyses*

If effect sizes showed moderate or greater inconsistency across studies as assessed by Higgin's I^2 [30], with values of 25%, 50% and 75% corresponding to low, moderate and high inconsistency, meta-regression was conducted to identify possible underlying sources of variation.

First, we examined symptom severity (as measured by the UPDRS-III), disease duration (years) and, for pain threshold, the assessment method (limits vs. constant/adjusted stimuli) as primary moderators, based on a rationale defined *a priori*. Greater symptom severity and longer disease duration likely to reflect increased neurodegeneration and therefore may be associated with a greater degree of abnormal pain perception. In addition, the methods of limits (where intensity increases to a pre-defined limit) involves a reaction time artefact (e.g. from pressing a button) which could artificially inflate threshold times and underestimate

true levels of pain selectively for PD patients due to motor impairment [13]. Conversely, the methods of constant stimuli/adjustment (where constant temperatures are gradually adjusted) [see 64] contains no reaction time component.

Secondary moderators were study gender composition, age, stimulus modality, PD side subject to pain testing (least/most affected), anatomic site subject to pain testing, and sample percentage experiencing PD-based pain complaints. These variables were examined to provide preliminary data on any potential moderating influence, as all have been suggested as possible influences [19]. Additionally, meaningful study validity criteria were assessed as moderators, such as case and control selection, criteria-based PD diagnosis, explicit mentioning of disallowing pain medications. Finally, where the endorsement of important validity criteria varied across studies, the influence of these criteria as potential moderators of effect size was also assessed.

2.8 Publication bias

Publication bias was examined through visual inspection of funnel plots of mean study ESs against standard errors. Any visual asymmetry resulting from the absence of small sample studies with small ESs can suggest possible publication bias. Asymmetry was also tested statistically with Egger's bias test [17] with $p<.05$ indicating asymmetry. If present, a revised effect size assuming the presence of publication bias was computed using the trim and fill method [16].

All analyses were performed using the *robumeta* package [20] in R [47].

3 Results

3.1 Study selection

3047 unique hits were identified through database searches, with 6 additional records identified through manual searching of reference lists. Following the initial screening of abstracts, 47 articles were retained for full text review of which 21 were excluded, resulting in a total of 26 studies retained for analysis (Figure 1).

-- FIGURE 1 ABOUT HERE --

3.2 Participant characteristics

The 26 retained studies provided aggregated data for N=1292 participants, consisting of 739 patients and 553 HCs. The mean study age (*k*=26 studies) was 63.8 years (*SD*=3.0, range of means=58.8-69.9 years) for the aggregated PD sample, and 62.4 years (*SD*=3.9, range of means=54.8-71.4 years) for the aggregated HC sample. The PD sample consisted of 35.7% females and the HC sample consisted of 42.7% of females (*k*=26).

For the PD sample, mean disease duration (*k*=25) was 7.1 years (*SD*=3.4, range of means= 1.8 - 15.5). Symptom severity (*k*=25) was most commonly measured with the original UPDRS-III Motor Examination scale [18] and was assessed during both ON (*k*=19; UPDRS-III *M*=21.8) and OFF (*k*=13; UPDRS-III *M*= 27.0) functional states. ON states were achieved with anti-Parkinson medication (*k*=18) or deep brain stimulation (*k*=1).

A diagnosis of PD was based on UKBBC (*k*=18), ICD-10:G20 (*k*=1), Gelb NINDS guidelines (*k*=1) or was simply reported as a clinical diagnosis of PD (*k*=6). Medication data (*k*=24) included a single study which used a medication-naïve patient sample [56], while 23 studies reported regular usage of anti-Parkinson medication (L-DOPA with/without other

medication) by some or all enrolled patients (*M*=95%, study range=67-100%). Most studies (*k*=22) specified a minimum level of cognitive functioning for inclusion in the study, with scores>=25 on the Mini-Mental State Examination being the most extensively used inclusion criterion (*k*=15).

Presence or absence of a primary chronic pain condition was reported by 13 studies. Of these, 12 reported no co-occurring chronic pain conditions and a single study reported that 2 patients may have exhibited chronic low back pain. The mean study percentage of PD patients reporting secondary pain complaints attributable to PD (*k*=18) was 48%.

3.3 Study characteristics

Of the 26 studies, 15 were conducted in Europe, 6 in Asia, 2 in Oceania and 1 in each of North America, South America and Africa. All studies reported the method of pain induction and functional state during testing. Pain induction methods comprised heat (*k*=16), electrical (*k*=10), cold (*k*=7), pressure (*k*=6) and laser (*k*=1). Location of pain induction (*k*=24) for patients was on the most affected body side (*k*=9), least affected side (*k*=3) or the left or right side (*k*=12), and was applied to the hand (*k*=13), forearm (*k*=10), leg (*k*=10), face (*k*=2), neck (*k*=1), head (*k*=1) or upper arm(*k*=1). Pain testing was performed during the ON state (*k*=19), the OFF state (*k*=18), with 11 studies having assessed pain during both states in a repeated-measures design. For ON states, pain testing was usually conducted within the first hour of treatment initiation, with the presence of ON states confirmed by a reduction in UPDRS-III motor scores in all 7 repeated-measures design studies that assessed this.

The majority of studies used pain threshold (*k*=21) as the method of pain assessment (*k*=11 method of limits, *k*=7 method of levels/adjustment, *k*=3 not stated), with other outcomes including pain intensity ratings (*k*=7), pain tolerance (*k*=3) and threshold for moderate pain (*k*=3), with several individual studies employing multiple induction and assessment methods.

Nine studies also assessed sensory threshold. Aside from one study that included only drug-naïve patients [56], OFF states were achieved by the withdrawal of dopaminergic medication, with pain testing usually taking place after a >= 12-hour washout period.

A summary of the key characteristics of the 26 individual studies is presented in Table 1.

3.4 Study validity criteria

Acceptable agreement across the two raters was found for most items (*Kappa*=0.77-1.00) except for those with high rates of endorsement (min *Kappa*=0.25). High endorsement rates can result in low kappa values due to marginal homogeneity [27] and thus percentage agreement across raters was computed, with resultant percentages indicating good agreement (>87%) for those items. Complete consensus was reached whenever any disagreement occurred (see Appendix S1 for all item ratings).

Ratings indicated methodological soundness (e.g., reporting of functional state during testing, complete data provided, clear description of procedures) for the majority of studies (>85% for most criteria). Most studies excluded patients with comorbid depression (77%) or somatosensory disorder (73%), with 42% explicitly specifying that use of pain medication (<24hrs) was an exclusion criterion. Low endorsement of 'selection of PD cases (23%) and controls (27%) validity criterion reflected limited detail on recruitment methods; although studies did generally state the name of the recruiting hospital and provide good descriptions of characteristics of controls, usually matching cases and controls either experimentally or by statistically controlling for age/gender (77%).

Some statistical inconsistencies were noted. One study [43] reported implausible pain thresholds (9.1-12.4˚C) for heat stimulation (values for other stimuli were plausible), and a further study [48] reported means and *SD*s for pain threshold highly inconsistent with

reported *p*-values (even when *SD*s were treated as *SEM*s), and so this specific data were excluded.

3.5 Meta-analysis results

3.5.1 *Pain threshold*

Pain threshold data was examined for *k*=20 studies comprising a total sample of N=926 (n=577 PD, n=473 HCs), with PD patents assessed during both OFF (*k*=14; N=728) and/or ON (*k*=13; N=617) states. Seven repeated-measures studies provided pain threshold data for both ON and OFF states.

Meta-analysis of pain threshold, aggregating data from both ON and OFF states, found significantly lower overall pain threshold (i.e., greater pain sensitivity) in PD patients compared to HCs (*SMD*=0.37, CI_{95}[0.16, 0.57], *p*=.001). Moderate to high heterogeneity (I^2=63%) was observed and *k*=16 of 20 studies reported lower pain thresholds in PD.

When separate meta-analyses were performed for ON and OFF state data, significantly lower pain thresholds in PD patients compared to HCs were found for the OFF state (*k*=14; *SMD*=0.51, CI_{95}[0.23, 0.79], *p*=.002), along with moderate-high heterogeneity (I^2=64%). For ON state data, lower overall pain threshold in PD was also found but with a reduced effect size (*k*=13; *SMD*=0.23, CI_{95}[0.02, 0.45], *p*=.04) and moderate heterogeneity (I^2=49%). A forest plot of pain threshold data for the OFF state is provided in Figure 2.

-- FIGURE 2 ABOUT HERE –

Funnel plots of pain threshold data revealed no obvious asymmetry for data from either ON or OFF states, corroborated by non-significant values for Egger's asymmetry test (OFF: z=0.30, p=.76; ON: z=0.42, p=.67), consistent with a possible lack of publication bias.

3.5.2 *Suprathreshold pain response*

Three studies reported pain tolerance data, and 3 other studies reported 'threshold to moderate pain' (where participants were told to withdraw from noxious stimulation when experiencing moderate pain). Both measures were collapsed to a single suprathreshold pain category to maximize power (three studies is insufficient for RVE analysis). The 6 combined studies provided aggregate data for 442 participants (n=288 PD patients, n=154 HCs). Pain assessment occurred during both ON (k=5) and OFF states (k=4), with 3 studies providing data for both states.

Meta-analysis of overall suprathreshold data found lower tolerance to suprathreshold pain (suggesting greater sensitivity) in PD patients, but this just failed to achieve statistical significance (*SMD*=0.30, CI_{95}[-0.01, 0.61], p=.06). Analysis of different functional states indicated lower tolerance to suprathreshold pain during OFF (*k*=4; *SMD*=0.44, *p*=.04) states but not during ON (*k*=5; *SMD*=0.15, *p*=.28) states. For analysis of OFF state data, population confidence intervals (and thus *p*-values) may be wider or narrower [58] as the adjusted *df*<4. Low heterogeneity was observed in all instances (I^2=4-27%).

A funnel plot of overall suprathreshold data suggested asymmetry due to the presence of a small sample study with a large *negative* effect size. Some indication of possible asymmetry emerged from Egger's test, which failed to achieve significance (but is also likely to be underpowered with only 6 studies), *z*=1.90, *p*=.054, A revised estimate using trim and fill

methods suggested a slightly larger effect size (*SMD*=0.36, *p*=.01) if publication bias is assumed.

3.5.3 *Other outcomes: Pain ratings and sensory threshold*

The adjusted *df* from RVE meta-analysis of pain ratings and sensory threshold were <4 (reflecting both limited number of studies using these assessment methods and data dependency), which precluded reliable estimation of ESs [58] for these outcomes.

3.6 Meta-regression analyses: pain threshold

Meta-regression analyses were conducted to identify underlying sources of heterogeneity in ESs across pain threshold studies (other pain outcomes were not examined due to limited data not meeting RVE requirements). Functional state (ON/OFF) was included as an additional variable in each analysis to maximise power by allowing use of all pain threshold data (i.e. from both ON and OFF states), and given that functional state during testing is likely to represent a substantial source of variation in ES across studies that should be controlled for as a possible confounder. In addition, including functional state as a moderator allows the direct assessment of whether differences across ON vs. OFF states identified in the meta-analysis (Section 3.5.1) were significant.

3.6.1 *PD severity*

We examined whether reduced pain threshold (greater pain sensitivity) in PD was exacerbated in patients with more advanced disease states, by including disease duration and UPDRS-III scores as moderators in separate analyses. Results indicated that differences

between PD and controls in pain threshold were not significantly influenced by disease duration (*k*=19; B=.035, *p*=.24) or UPDRS-III symptom severity (*k*=19; B=.006, p=.71).

Results also indicated that effect size was significantly larger (*k*=19; ΔSMD=0.33, CI_{95}[0.02, 0.64], *p*=.039) for OFF (B=0.58) than ON (B=0.25) states. This pattern of results was reproduced (*k*=19; ΔSMD=0.33, CI_{95}[0.02, 0.66], p=.041), when analysis was restricted to ON states achieved through dopamine medication only (i.e. the single deep brain stimulation study was excluded).

3.6.2 *Method of assessment*

Entering assessment method (limits vs. levels/adjustment) as a moderator in meta-regression of pain threshold revealed that the difference in pain threshold between PD patients and controls was larger when the method of levels/adjustment was used, although this failed to reach statistical significance (*k*=18; ΔSMD=.34, *p*=.061).

3.6.3 *Secondary moderators*

Separate meta-regression analyses were conducted to explore other moderators specified in section 2.7.3. As 15 pain threshold studies explicitly stated the use of established diagnostic criteria and 5 studies did not provide information, we also examined this variable as a potential moderator. Given limited data for certain anatomic categories, we collapsed data to form two broad anatomic categories of arm (forearm, upper arm, hand) and leg (leg, foot). For the multiple categorical variable of stimulus modality, a no-intercept model was analysed so that each coefficient represented the absolute ES for each stimulus modality (rather than the difference in ES between that modality and an arbitrary reference modality).

No evidence was found for moderating effects of studies' gender composition (*k*=20; *p*=.38), mean study age (*k*=20; *p*=.62), affected vs. non-affected side tested (*k*=9; *p*=.91), anatomic site tested (*k*=17; *p*=.43) or diagnostic criteria provided (*k*=20; p=.55). For stimulus modality (k=20), however, PD patients demonstrated lower pain threshold than HCs in response to cold (*SMD*=0.62, *p*=.011), electrical (*SMD*=0.53, *p*<.001) and pressure (*SMD*=0.41, *p*=.055) stimuli, but not heat stimuli (*SMD*=-0.05, *p*=.79). PD-related pain could not be reliably assessed as a moderator, as the adjusted *df* was <4 [58].

3.6.4 *Study validity criteria*

Given low endorsement for validity criteria of selection of cases/controls and reporting of pain medication use (Section 3.4), these variables were entered as moderators in separate meta-regression analyses of pain threshold. Neither case selection (*p*=.79) or control selection (*p*=.68) significantly moderated the ES. Differences in pain threshold between PD patients and controls were amplified in studies explicitly stating that participants were not using pain medication, although this did not achieve statistical significance (*ΔSMD*=.40, *p*=.052).

3.7 Repeated-measures studies comparing ON vs. OFF states

As previous analyses (Section 3.6.1) revealed that differences between PDs and controls were reduced during the ON state, we conducted a stricter evaluation by repeating the analysis including only the 7 studies that directly compared ON vs. OFF in a repeated-measures designs to ensure superior control of confounds. Results were in line with previous findings (section 3.6.1), with differences in pain threshold between PD patients and HCs attenuated during ON states (*k*=7; ΔSMD =-0.25, CI_{95}[-0.11, -0.38], *p*=.004). Removal of two

studies that did not randomize/ counterbalance ON/OFF state or failed to test HCs at equivalent intervals, had little impact on results (k=5; ΔSMD=-0.22, p=.045). Only 4 studies provided L-DOPA dosages during ON states, which was not sufficient to meet requirements for RVE meta-regression.

4 Discussion

The current meta-analysis is the first to examine whether patients with PD exhibit increased pain sensitivity compared to HCs and to investigate potential moderators. Our comprehensive analysis of 26 studies, primarily assessing pain threshold, with a combined total of 739 PD patients and 553 controls yielded several key findings: (1) Overall pain threshold was lower in PD patients (indicating greater pain sensitivity) compared to HCs; (2) Suprathreshold pain was lower in PD patients, although this narrowly failed to reach significance; (3) Abnormal pain thresholds in people with PD during OFF states (*SMD*=0.51) were significantly diminished, but not completely normalized during ON states (*SMD*=0.23) produced by dopaminergic medication; (4) Abnormal pain thresholds were not significantly influenced by symptom severity, disease duration, sex or age; (5) While most (16/20) individual studies indicated lower pain threshold in PD, moderate to high variation in effect sizes suggests that other, unidentified variables could influence abnormal pain responses in PD.

4.1 Pain hypersensitivity in PD and clinical implications

Results from our meta-analysis provide evidence that patients with PD demonstrate greater sensitivity to noxious stimulation compared to HCs, which seem to be independent of age and sex, and which occur for most types of aversive stimuli. Although no overall differences

were found for heat stimulation, the post-hoc nature of this result means any conclusions of modality-specific nociceptive processing abnormalities in PD should be made extremely cautiously and would require independent replication.

Taken together, these results suggest that the increased prevalence and intensity of clinical pain complaints in PD could be, at least in part, influenced by abnormal nociceptive processing. In particular, these results could explain the increased prevalence of non-musculoskeletal pain complaints (e.g., neuropathic pain), which do not obviously directly result from motor dysfunction. Although care must be taken in translating effect sizes from experimentally-induced pain to real-life pain experiences, the fact that an *SMD*=0.51 (in medication-free OFF states) can be classified as a moderate effect [12], provides some preliminary indication that the impact of PD on pain complaints outside of the laboratory may not be trivial.

There is also some tentative evidence to suggest that the true extent of increased pain sensitivity could be underestimated by the moderate effect size we observed. Studies that explicitly stated that participants were not receiving pain medication (with PD patients generally being more likely to regularly use painkillers) were linked to a larger effect size (an *SMD* increase by 0.40). In addition, studies employing the methods of levels/adjustment, which has been argued to give a more accurate estimate of pain threshold than the method of limits due to a reduced reaction time artefact, also demonstrated a larger effect size (an *SMD* increase by 0.34). It is important that these findings are treated cautiously, as although suggestive, neither subgroup analysis reached statistical significance (p=.052-.061).

4.2 Role of dopamine

The partial normalisation of the atypical pain thresholds in PD resulting from dopaminergic medication appears to be a robust finding, which was observed when all studies were examined and when only repeated-measures studies, which provide superior control of potential confounds, were included. This partial normalisation of pain threshold has a number theoretical and clinical implications which warrant further elaboration.

First, this finding offers indirect evidence for an underlying role of dopamine depletion in pain hypersensitivity in PD. Although identifying exact underlying mechanisms is difficult from the available data, dopamine could elicit pain hypersensitivity either indirectly through modulatory effects on affective pain processing and/or directly by affecting neuronal activity at key pain-modulating areas in the brain such as the thalamus, basal ganglia, insula, anterior cingulate cortex and periaqueductal grey [19, 31]. Reduced dopaminergic neurotransmission may impair natural analgesia through a decreased activation of dopamine-mediated pain inhibitory pathways. These descend from the substantia nigra to the substantia gelatinosa in the spinal cord and inhibit transmission of ascending nociceptive signals [19]. This direct role of dopamine is consistent with PET studies in healthy participants that show an association between greater subjective pain and decreased dopamine activity [13], the diminished pain response seen in schizophrenia [53] a disorder linked to aberrant dopaminergic neurotransmission, and evidence from animal models suggesting a role of dopamine in chronic regional pain syndrome [63]. Experimental research on pain in PD patients assessing the effect of pro-dopaminergic and antidopaminergic states or medications could help further elucidate the role of dopamine in pain perception.

Second, if attenuation of pain can be achieved through dopaminergic medication, this suggests that the development of classes of novel compounds that efficiently target dopamine pain-inhibitory pathways may have potential as effective analgesics. Such

compounds may be effective analgesics both for PD and for other painful disorders linked to disrupted endogenous dopamine activity such as fibromyalgia, burning mouth syndrome and painful diabetic neuropathy [31, 63]. Furthermore, if the suggestion that the underuse of conventional painkillers in PD patients is attributable to poor efficacy in this group [44], such medications could provide potentially superior alternatives. The utility of such analgesics could even extend to conventional treatment in healthy individuals with pain. While the role of opioids and non-dopaminergic (e.g. noradrenergic or serotoninergic) pathways is well recognised, the current findings further suggest a meaningful role for dopamine-mediated analgesia and may provide the impetus for further study involving preclinical models and neuroimaging techniques in humans.

4.3 Partial pain threshold normalization

The fact that dopamine medication diminished but did not appear to completely normalise pain threshold, suggests that additional mechanisms are likely to contribute to pain hypersensitivity in PD. Although it is difficult to identify such mechanisms from the current available data, these could include a loss of epidermal nerve fibres [43] or deficiencies in other, non-dopaminergic pain pathways. An alternative explanation is that pain hypersensitivity *is* entirely mediated by dopamine deficiency in PD but that study medication dosages were insufficient to restore dopamine neurotransmission to normal physiological levels. Due to insufficient available data, we were not able to assess whether higher L-DOPA dosages were associated with greater normalisation of pain threshold.

4.4 Independence of motor impairment and pain

One notable finding was that pain sensitivity did not increase with increasing disease severity or duration. While this contrasts with clinical surveys which have shown the frequency and intensity of pain to be greater in advanced-stage compared to early-stage PD [59], this research refers primarily to musculoskeletal pain. While disease progression would be expected to intensify this type of pain due to increasing muscle rigidity or postural abnormalities [13], our findings suggest that changes in sensitivity to noxious input may occur early on and be relatively independent of motor function degradation.

4.5 Limitations

Whilst these data provide novel insights into altered pain perception in PD, some limitations should be noted. Firstly, findings are based primarily on pain threshold which was the most commonly studied pain outcome. Although an established measure of pain sensitivity, pain threshold represents pain at the lower end of the intensity continuum and cannot be automatically generalised to more intense levels of clinical pain. Second, although adequate data was available for meta-regression, genuine moderating effects of variables (e.g. disease duration) that were non-significant cannot be dismissed, and may be detectable with more available data; especially if the magnitude of these effects is small. Third, although exclusion of PD patients with cognitive impairment in primary studies was necessary to maximise adherence to experimental requirements, current findings should be necessarily restricted to PD patients who have relatively preserved overall cognition [21].

4.6 Future research directions

Despite these limitations, the current findings provide strong support that individuals with PD exhibit greater sensitivity to noxious stimuli than HCs, based on laboratory studies that

provide a control of potential confounders not easily achievable in clinical settings. Future studies are needed to help establish whether pain hypersensitivity in PD extends to suprathreshold levels of pain, and insights may also be gained from the use of ischemic and dermal capsaicin experimental pain models that evoke several aspects of chronic pain whilst preserving strict experimental control [50]. More research involving preclinical models and neuroimaging techniques in humans would also help to elucidate potential mechanistic pathways underlying altered pain perception in PD.

4.7 Conclusions

To the authors' knowledge, this is the only published meta-analysis of studies comparing PD patients with healthy controls in their response to controlled experimental pain stimulation. Results indicate significantly lower pain threshold in PD patients (indicative of greater pain) in the OFF state compared to controls. This was partially (but not completely) normalized by dopaminergic medication, suggesting that disruption of dopamine pain pathways may contribute to abnormal pain processing. These findings suggest that PD may confer a hypersensitivity to nociceptive information that could both exacerbate the musculoskeletal pain resulting from motor rigidity and abnormal posture control, and contribute to the less common but nevertheless troubling non-musculoskeletal pain complaints that occur in PD.

Acknowledgements

We are especially grateful to Drs Gergely Orsi, Yelena Granovsky, Jon Stoessl, Maria Nolano, Tomohiko Nakamura, Masanaka Takeda, Janosch Priebe for their rapid and exceptionally helpful responses to requests for additional study data. We are also extremely grateful to

Professor John Lees and Dr Alastair Noyce of University College London for their invaluable advice and extremely helpful commentary on the manuscript.

Online Supplementary Material

Appendix S1. Endorsement of validity criteria (1=criteria satisfied, 0=criteria not satisfied)

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Allen at al (2016)	1	1	0	0	0	0	1	1	1	1	1	1	1	0	1	1	0	0	0
Mylius et al (2016)	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0
Priebe et al (2016)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1
Ascherman et al (2015)	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	0
Chen et al (2015)	0	1	0	1	1	0	1	1	1	1	1	1	0	1	1	1	0	1	1
Grashorn et al (2015)	1	1	0	0	1	1	1	1	1	1	1	1	1	0	1	1	1	1	0
Tan et al (2015)	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
Takeda et al (2014)	1	1	0	0	1	0	0	1	1	1	1	1	1	1	1	1	0	1	0
Granovsky et al (2013)	1	1	0	0	0	1	1	1	1	1	1	1	0	1	1	1	0	0	1
Hara et al (2013)	0	1	0	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1
Ciampi de Andrade et al (2012)	1	1	0	0	1	1	1	1	1	1	0	1	1	0	1	1	0	1	1
Stamelou et al (2012)	1	1	0	0	1	1	1	1	1	0	1	1	0	1	1	1	1	1	1
Vela et al (2012)	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
Maruo et al (2011)	1	1	1	0	1	1	1	1	1	0	1	1	1	1	1	1	0	0	0
Mylius et al (2011)	1	1	0	0	0	1	1	1	1	0	1	1	1	1	1	1	1	1	1
Zambito-Marsala et al (2011)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1
Nandhagopal et al (2010)	1	0	0	0	0	1	1	1	1	0	1	1	1	0	1	1	1	1	1
Mylius et al (2009)	1	1	0	0	0	1	1	1	0	0	1	1	1	1	1	1	1	1	1
Lim et al (2008)	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1
Nolano et al (2008)	1	1	0	0	1	1	1	1	1	1	1	1	0	1	1	1	0	0	1
Gerdelat-Mas et al (2007)	1	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Schestatsky et al (2007)	0	1	1	1	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1
Vela et al (2007)	1	1	0	1	1	1	1	1	1	0	1	1	0	1	1	1	0	1	1
Brefel-Courbon et al (2005)	1	1	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1	0	1
Djaldetti et al (2004)	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1
Massetani et al (1989)	1	1	0	0	0	1	1	1	1	0	1	0	0	1	1	1	0	1	0
Mean Item Endorsement	0.88	0.96	0.23	0.27	0.69	0.88	0.92	1	0.92	0.73	0.96	0.96	0.77	0.85	0.88	0.92	0.42	0.77	0.73

Item Key: 1-Was there a clear specification of study objectives?; 2-Is the definition of PD adequate?; 3-Representativeness of PD cases; 4-Selection of Controls; 5-Definition of Controls; 6-Was there a clear description of the inclusion and exclusion criteria?; 7-Was the method of pain assessment clearly described?; 8-Was the method of pain induction clearly reported?; 9-Was it stated whether testing occurred in ON of OFF period?; 10-Comparability of cases and controls; 11-Were relevant participant characteristics adequately described?; 12-Was PD severity reported?; 13-Was cognitive impairment assessed?; 14-If any attrition, was drop-out relatively equal for both groups?; 15-Were complete outcome data available?; 16-Were statistics reported for significant and non-significant outcomes?; Were exclusion criteria reported for: 17-use of pain modifying medication, 18-presence of depression or other comorbid psychiatric/neurological diagnosis, 19- somatosensory disorder.

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Figure captions

Figure 1. PRISMA flow diagram

Figure 2. Forest plot of pain threshold, with box sizes proportional to study weights (for studies with multiple outcomes, weights are divided evenly across outcomes).

Table 1. Summary of included studies.

Study	N - PD	Duration years	UPDRS-III	ON/OFF state during pain testing	Usual Medication	N - CON	Modality
Priebe et al (2016) [45]	23	8.1	18.4 (OFF)	OFF ON	Mixed (L-DOPA=1; DA agonists =5; L-DOPA + DA agonists =17; MAO inhibitors=9; COMT inhibitors=2; NMDA blockers=5)	23	Heat Electrical
Mylius et al (2016) [40]	14	1.8	22.8 (ON)	OFF	NS but inc. L-DOPA	27	Heat Electrical
Allen at al (2016) [1]	26	-	27.3[b] (ON)	ON	NS	11	Pressure (*ty* *not stated*)
Ascherman et al (2015)-a[3]	6	6.20	11.2 (ON)	ON	Mixed (levodopa, dopamine agonists, MAO and COMT-inhibitors)	6	Heat
Ascherman et al (2015)-b [3]	6	5.50	15.8 (ON)	ON	Mixed (as above)	6[a]	Heat
Chen et al (2015) [10]	72	4.90	29.5 (OFF) 23.1 (ON)	OFF ON	L-DOPA	35	Electrical
Grashorn et al (2015) [26]	25	3.70	24.1 (OFF) 20.7 (ON)	OFF ON	Mixed (L-DOPA=4, L-DOPA+ MAO inhibitors=2, L-DOPA+ DA agonists=1; DA agonists =7; DA agonists+MAO Inhibitors =9; MAO inhibitors=2)	30	Heat Cold presso
Tan et al (2015) [56]	14	2.50	21.8 (OFF)	OFF	None	17	Heat
Takeda et al (2014) [55]	23	5.60	27.0 (ON)	ON	Mixed (L-DOPA=4, L-DOPA+ DA agonists=11, MAO inhibitors=8)	12	Electrical
Hara et al (2013) [28]	42	6.50	21.6 (ON)	ON	Mixed (L-DOPA, DA agonists, MAO inhibitors, catechol-Omethyl transferase and amantadine)	17	Electrical
Granovsky et al (2013) [25]	23	6.30	23.6 (ON)	OFF ON	Mixed (L-DOPA=11, DA agonists=17, MAO inhibitors=19, Anticholinergics =8, Amantadine=14)	19	Heat Pressure (*v* *Frey filame*
Vela et al (2012) [60]	18	11.60	34.5 (OFF) 22.1 (ON)	OFF ON	Mixed (L-DOPA, DA agonists)	18	Pressure (*algometer*) Heat Cold
Ciampi de Andrade et al (2012) [11]	25	15.10	42.7 (OFF) 25.8 (ON – via DBS)	OFF ON	L-DOPA	35	Heat Cold Pressure (*v* *Frey filame*
Stamelou et al (2012) [51]	19	6.70	22.4 (ON)	OFF	L-DOPA (no details on other medications)	17	Heat Electrical

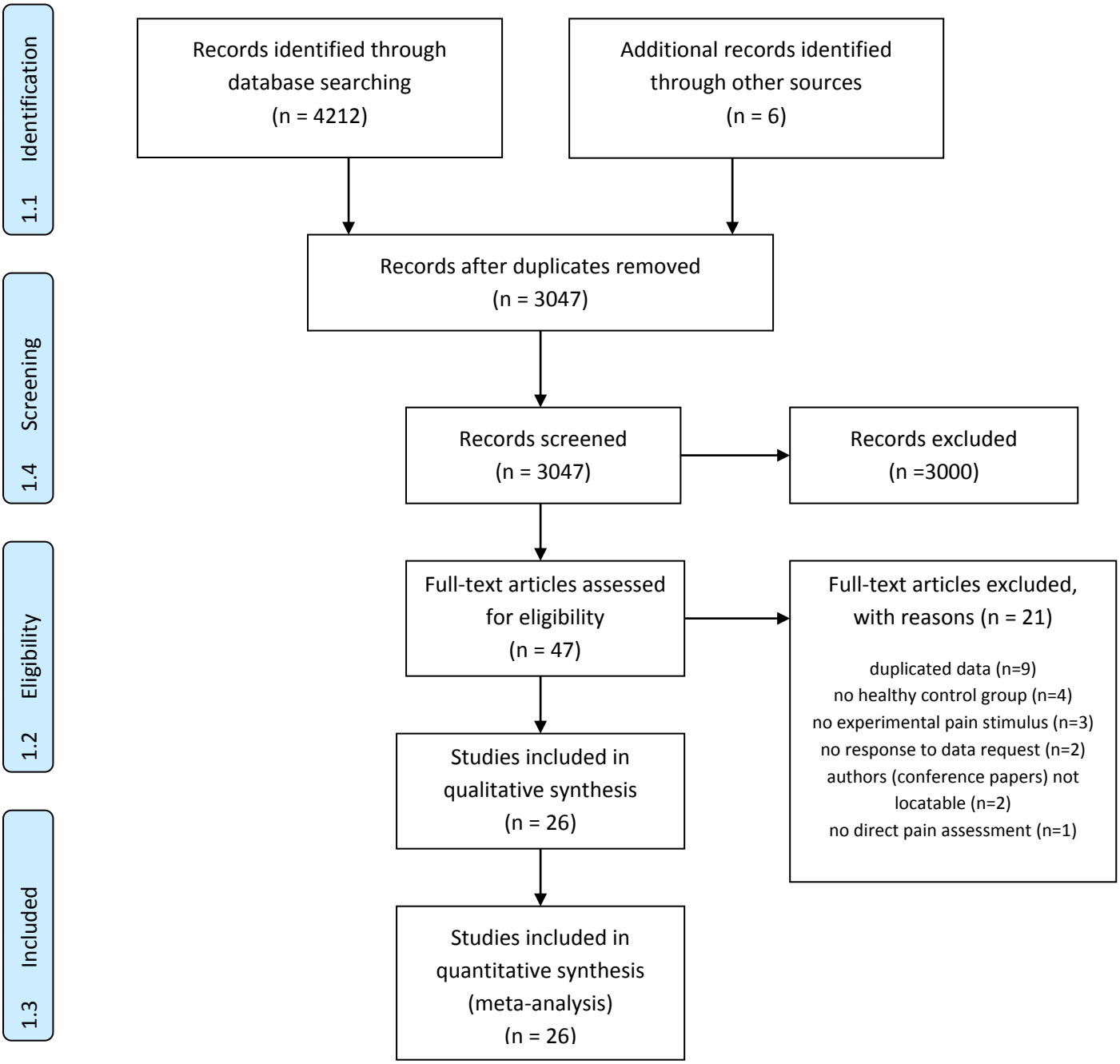
Study	N - PD	Duration years	UPDRS-III	ON/OFF state during pain testing	Usual Medication	N - CON	Modality
Mylius et al (2011) [38]	29	7.40	25.6 (ON)	OFF	L-DOPA (no details on other medications)	27	Electrical Heat
Maruo et al (2011) [34]	17	15.50	36.3 (ON)	ON	L-DOPA, DA agonists (no details on other medications)	14	Cold Heat
Zambito-Marsala et al (2011) [65]	106	5.70	23.5 (OFF)	OFF	Mixed (L-DOPA=38; DA agonists =19; L-DOPA + DA agonists =49)	51	Electrical
Nandhagopal et al (2010) [41]	12	9.40	28.8 (OFF) 15.0 (ON)	OFF ON	Mixed (L-DOPA with/without other medication=12)	13	Heat
Mylius et al (2009) [39]	15	11.00	28.3 (OFF)	OFF	Mixed	18	Heat Electrical
Nolano et al (2008) [43]	18	7.60	26.6 (ON)	ON	Mixed (L-DOPA with/without other medication=14, None=4)	54	Cold Heat Pressure (*nylon monofilame*
Lim et al (2008) [32]	50	4.38	29.6 (OFF) 21.3 (ON)	OFF ON	L-DOPA (no details on other medications)	20	Cold presso
Gerdelat-Mas et al (2007) [23]	13	7.30	21.2 (OFF) 10.8 (ON)	OFF ON	Mixed (L-DOPA and/or DA agonists)	10	Electrical
Schestatsky et al (2007)-a [48]	9	5.40	17.1 (NS)	OFF ON	NS but inc. L-DOPA	9	Heat Laser
Schestatsky et al (2007)-b [48]	9	6.00	19.1 (NS)	OFF ON	NS but inc. L-DOPA	9[a]	Heat Laser
Vela et al (2007)-a [61]	25	11.38	24.6 (ON)	ON	NS	25	Pressure (*algometer*)
Vela et al (2007)-b [61]	25	4.72	19.9 (ON)	ON	NS	25[a]	Pressure (*algometer*)
Brefel-Courbon et al (2005) [5]	9	9.60	25.0 (OFF) 15.0 (ON)	OFF ON	Mixed (L-DOPA and/or DA agonists)	9	Cold presso
Djaldetti et al (2004) [15]	51	5.30	24.0 (OFF)	OFF	Mixed (L-DOPA and/or DA agonists)	28	Heat
Massetani et al (1989) [35]	15	4.10	NA	ON	Mixed (L-DOPA with or without peripheral decarboxylase inhibitor=10, drug free=5)	8	Electrical
TOTAL for 26 studies	739	*M*=7.10 years	ON: *M*=22.2 yrs OFF: *M*=27.0 yrs	ON=19; OFF=18	L-DOPA with/without others=23 Not Stated =2 None=1	553	Heat=16; Electrical=1 Cold=7; Pressure=6; Laser=1

Key: NS=Not Stated, NFR=Nociceptive Flexion Reflex, DA=Dopamine, MAO=Monoamine oxidase, COMT=Catechol-O-methyltransferase, NMDA=N-methyl-D-aspartate

[a]Same control group used for '-a' and '-b' studies

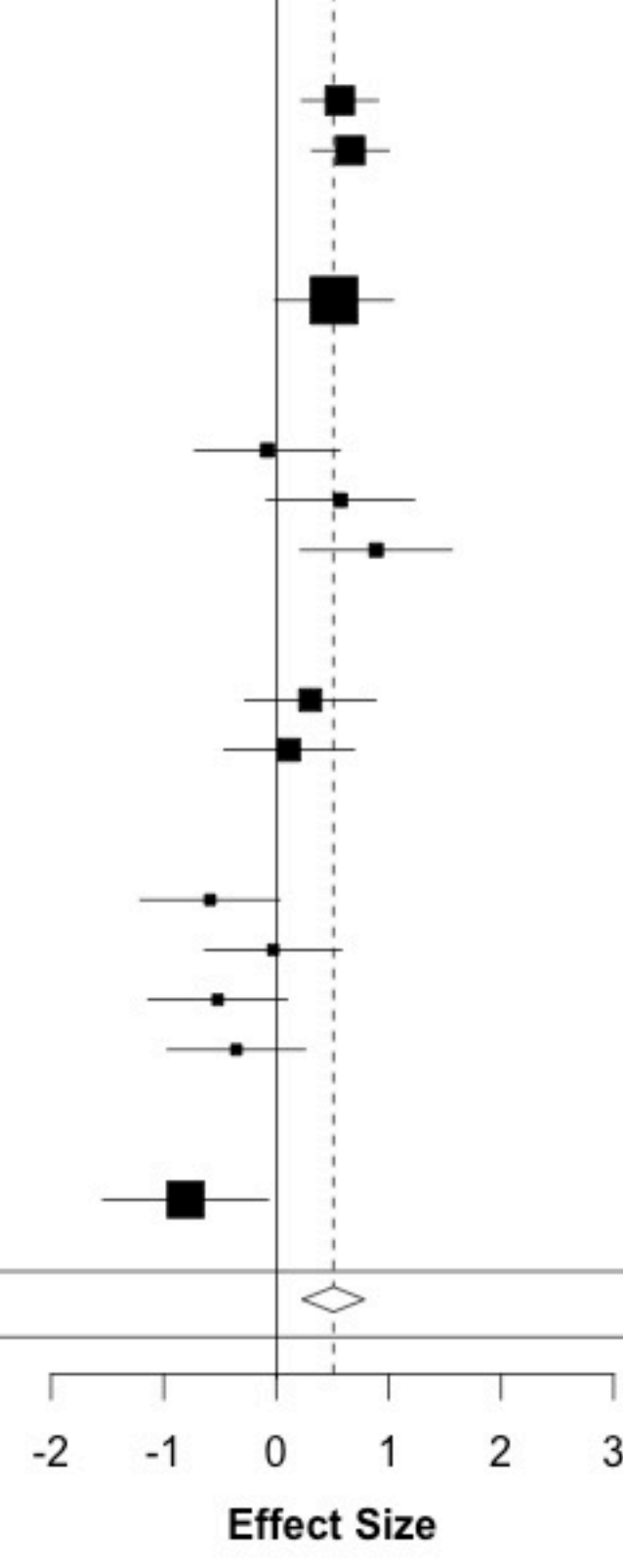
[b]Estimated from MDS-UPDRS-III score of 33.8 using conversion formula [24]

Figure 1. PRISMA flow diagram



Forest Plot

Studies	Effect Size	Weight
Gerdelat-Mas et al (2007)	1.12	2.74
Mylius et al (2009)		
Electric (Nociceptive Flexion Response)	1.45	1.11
Electric	0.72	1.11
Heat	0.89	1.11
Brefel-Courbon et al (2005)	1.01	2.43
Vela et al (2012)		
Pressure - most affected side	0.84	0.59
Heat - most affected side	0.81	0.59
Cold - most affected side	0.68	0.59
Pressure - least affected side	0.93	0.59
Heat - least affected side	0.65	0.59
Cold - least affected side	0.68	0.59
Stamelou et al (2012)		
Electric (Nociceptive Flexion Response)	1.28	1.18
Electric	0.67	1.18
Heat	0.21	1.18
Ciampi de Andrade et al (2012)		
Pressure	1.29	1.42
Heat	0.33	1.42
Cold	0.49	1.42
Mylius et al (2011)		
Electric (Nociceptive Flexion Response)	1.10	1.40
Electric	0.58	1.40
Heat	0.43	1.40
Djaldetti et al (2004)	0.66	4.56
Zambito-Marsala et al (2011)		
Hand	0.57	2.61
Foot	0.66	2.61
Lim et al (2008)	0.51	4.29
Mylius et al (2016)		
Heat	-0.08	1.22
Electric	0.57	1.22
Electric (Nociceptive Flexion Response)	0.89	1.22
Priebe et al (2016)		
Heat	0.30	2.01
Electric (Nociceptive Flexion Response)	0.11	2.01
Granovsky et al (2013)		
Heat - most affected side	-0.59	0.96
Pressure - most affected side	-0.03	0.96
Heat - least affected side	-0.52	0.96
Pressure - least affected side	-0.35	0.96
Tan et al (2015)	-0.81	3.31
Summary Effect [95% CI]	**0.51**	**[0.23, 0.79]**



(Higher pain threshold in PD)

(Lower pain threshold in PD)