



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

Trevor Thompson<sup>a,\*</sup>, Katy Gallop<sup>b</sup>, Christoph U. Correll<sup>c,d</sup>, Andre F. Carvalho<sup>e</sup>, Nicola Veronese<sup>f</sup>, Ellen Wright<sup>g</sup>, Brendon Stubbs<sup>h,i</sup>

<sup>a</sup> Faculty of Education and Health, University of Greenwich, London SE9 2UG, UK

<sup>b</sup> Acaster Consulting, London SE3 7HU, UK

<sup>c</sup> Department of Psychiatry, The Zucker Hillside Hospital, Northwell Health, Glen Oaks, NY 11004, USA

<sup>d</sup> Department of Psychiatry and Molecular Medicine, Hofstra Northwell School of Medicine, Hempstead, NY 11549, USA

<sup>e</sup> Department of Clinical Medicine and Translational Psychiatry Research Group, Faculty of Medicine, Federal University of Ceará, Fortaleza, CE, Brazil

<sup>f</sup> Institute for Clinical Research and Education in Medicine, I.R.E.M., Padova, Italy

<sup>g</sup> Department of Primary Care and Public Health Sciences, King's College London, London SE1 3QD, UK

<sup>h</sup> Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London SE5 8AZ, UK

<sup>i</sup> Health Service and Population Research Department, King's College London, London SE5 8AF, UK

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### 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 1292 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,  $p = 0.06$ ). 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.

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\* Corresponding author.

E-mail address: [t.thompson@gre.ac.uk](mailto:t.thompson@gre.ac.uk) (T. Thompson).

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## 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 (Broen et al., 2012), 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 (Nègre-Pagès et al., 2008). Pain often appears early in the development of PD and may be present years before clinical diagnosis (Schrage et al., 2015). Pain has been rated as the most burdensome non-motor symptom (Chaudhuri and Odin, 2010), and contributes to PD-related disability, sleep disturbance, and impaired quality of life (Chaudhuri and Schapira, 2009; Fil et al., 2013; Quittenbaum and Grahn, 2004). 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 (Chaudhuri and Schapira, 2009). Nevertheless, pain is a frequently overlooked symptom of PD, often unreported by patients unaware that painful symptoms are linked to the disease (Mitra et al., 2008), and consequently under-treated (Broen et al., 2012) which can increase the overall burden of PD. This is especially unfortunate given that pain represents a non-motor symptom that is eminently treatable (Chaudhuri et al., 2010).

While pain in PD is often precipitated by muscular rigidity and/or postural abnormalities (Ford, 2010), neurodegenerative processes could potentially affect not only motor function, but also peripheral (Nolano et al., 2008) and brain (Fil et al., 2013) 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 (Fil et al., 2013). A role of dopamine in pain is consistent with reduced pain sensitivity seen in schizophrenia (Stubbs et al., 2015), 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 (Cury et al., 2016).

If pain processing is affected centrally in PD, as hypothesised, this could result in a generalised hypersensitivity to noxious sensations (Cury et al., 2016), which may influence the onset of and/or exacerbate painful symptoms in PD (Broen et al., 2012). 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 (Chen et al., 2015; Lim et al., 2008; Mylius et al., 2009), others have failed to find such an effect (Granovsky et al., 2013; Massetani et al., 1989; Vela et al., 2007). This inconsistency may be influenced by methodological differences across studies, including variation in sample size, dopaminergic and analgesic medications, disease duration and symptom severity (Fil et al., 2013; Priebe et al., 2016). 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 were conducted in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement (Moher et al., 2009) and the *Meta-analysis of Observational Studies in Epidemiology* (MOOSE)

guidelines (Stroup et al., 2000) 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 (Aschermann et al., 2015; Granovsky et al., 2013; Hara et al., 2013; Nandhagopal et al., 2010; Nolano et al., 2008; Takeda et al., 2013) 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 (Apkarian et al., 2005). 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 were performed by two authors (TT, KG), on a standardized form adapted from our previous

studies (Stubbs et al., 2015; Thompson et al., 2016). 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 (Lipsey and Wilson, 2001). 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 (Aschermann et al., 2015; Schestatsky et al., 2007; Vela et al., 2007), e.g. with/without dyskinesia, and were treated as separate studies in the analysis (Borenstein et al., 2009). Second, for one study that used a wide range of temperatures (Nandhagopal et al., 2010), 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 (Aschermann et al., 2015; Chen et al., 2015), the lowest frequency was arbitrarily selected, as there appears to be no persuasive evidence for a frequency effect (Chen et al., 2015). 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 (Wells et al., 2008), and methodological soundness with 14 items based on Cochrane Collaboration principles as reviewed by Deeks et al. (2003) (see Table 1). Overall scores were not computed due to concerns over their interpretability (Deeks et al., 2003), 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 (Borenstein et al., 2009). Hedges' *g* is equivalent to Cohen's *d*, but corrects for bias in small samples. Effect sizes can be interpreted as 0.20, 0.50 and 0.80 corresponding to small, medium and large effects respectively (Cohen, 1988).

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 (Stubbs et al., 2015; Thompson et al., 2016). 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 (Hedges et al., 2010),

**Table 1**  
Summary of included studies.

Study	N-PD	Duration years	UPDRS-III	ON/OFF state during pain testing	Usual Medication	N-CON	Modality	Testing Site	Pain Measure
Priebe et al. (2016)	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	Forearm Leg	Pain Threshold Pain Threshold (NFR) Pain Intensity EMG response Pain Threshold Pain Threshold (NFR)
Mylius et al. (2016)	14	1.8	22.8 (ON)	OFF	NS but inc. L-DOPA	27	Heat Electrical	Forearm Leg	Pain Threshold Pain Threshold (NFR)
Allen et al. (2016)	26	–	27.3 <sup>b</sup> (ON)	ON	NS	11	Pressure ( <i>type not stated</i> ) Heat	Upper Arm Leg	Pain Threshold
Aschermann et al. (2015)	6	6.20	11.2 (ON)	ON	Mixed (levodopa, dopamine agonists, MAO and COMT-inhibitors)	6	Heat	Forearm	Pain Threshold (for moderate pain) Pain Intensity
Aschermann et al. (2015)	6	5.50	15.8 (ON)	ON	Mixed (as above)	6 <sup>a</sup>	Heat	Forearm	Pain Threshold (for moderate pain) Pain Intensity
Chen et al. (2015)	72	4.90	29.5 (OFF) 23.1 (ON)	OFF ON	L-DOPA	35	Electrical	Hand	Sensory Threshold Pain Threshold Pain Tolerance
Grashorn et al. (2015)	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 pressor	Forearm Leg	Pain Threshold (for moderate pain) Pain Intensity
Tan et al. (2015)	14	2.50	21.8 (OFF)	OFF	None	17	Heat	Forearm	Sensory Threshold Pain Threshold Pain Intensity
Takeda et al. (2014)	23	5.60	27.0 (ON)	ON	Mixed (L-DOPA = 4, L-DOPA+ DA agonists = 11, MAO inhibitors = 8)	12	Electrical	Hand Leg	Pain Threshold (for moderate pain)

Table 1 (Continued)

Study	N-PD	Duration years	UPDRS-III	ON/OFF state during pain testing	Usual Medication	N-CON	Modality	Testing Site	Pain Measure
<a href="#">Hara et al. (2013)</a>	42	6.50	21.6 (ON)	ON	Mixed (L-DOPA, DA agonists, MAO inhibitors, catechol-Omethyl transferase and amantadine)	17	Electrical	Face	Pain Threshold
<a href="#">Granovsky et al. (2013)</a>	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 ( <i>von Frey filaments</i> )	Hand Forearm	Pain Threshold Pain Intensity
<a href="#">Vela et al. (2012)</a>	18	11.60	34.5 (OFF) 22.1 (ON)	OFF ON	Mixed (L-DOPA, DA agonists)	18	Pressure ( <i>algometer</i> ) Heat Cold Heat Cold Pressure ( <i>von Frey filaments</i> )	Neck Head Hand Leg Hand	Pain Threshold
<a href="#">Ciampi de Andrade et al. (2012)</a>	25	15.10	42.7 (OFF) 25.8 (ON - via DBS)	OFF ON	L-DOPA	35	Heat Cold Heat Cold Pressure ( <i>von Frey filaments</i> )	Hand	Sensory Threshold Pain Threshold Pain Intensity
<a href="#">Stamelou et al. (2012)</a>	19	6.70	22.4 (ON)	OFF	L-DOPA (no details on other medications)	17	Heat Electrical	Forearm Leg	Pain Threshold (NFR) Pain Threshold Pain Threshold (NFR)
<a href="#">Mylius et al. (2011)</a>	29	7.40	25.6 (ON)	OFF	L-DOPA (no details on other medications)	27	Electrical Heat	Forearm Leg	Pain Threshold (NFR)
<a href="#">Maruo et al. (2011)</a>	17	15.50	36.3 (ON)	ON	L-DOPA, DA agonists (no details on other medications)	14	Cold Heat	Hand	Sensory Threshold Pain Threshold
<a href="#">Zambito et al. (2011)</a>	106	5.70	23.5 (OFF)	OFF	Mixed (L-DOPA = 38; DA agonists = 19; L-DOPA + DA agonists = 49)	51	Electrical	Hand Foot	Sensory Threshold Pain Threshold Pain Tolerance

Nandhagopal et al. (2010)	12	9.40	28.8 (OFF) 15.0 (ON)	OFF ON	Mixed (L-DOPA with/without other medication = 12)	13	Heat	Forearm	Pain Intensity Pain Unpleasantness
Mylius et al. (2009)	15	11.00	28.3 (OFF)	OFF	Mixed	18	Heat Electrical	Forearm Leg	Pain Threshold Pain Threshold (NFR)
Nolano et al. (2008)	18	7.60	26.6 (ON)	ON	Mixed (L-DOPA with/without other medication = 14, None = 4)	54	Cold Heat Pressure ( <i>nylon monofilament</i> )	Hand Foot	Sensory Threshold Pain Threshold
Lim et al. (2008)	50	4.38	29.6 (OFF) 21.3 (ON)	OFF ON	L-DOPA (no details on other medications)	20	Cold pressor	Hand	Pain Threshold Pain Tolerance
Gerdelat-Mas et al. (2007)	13	7.30	21.2 (OFF) 10.8 (ON)	OFF ON	Mixed (L-DOPA and/or DA agonists)	10	Electrical	Leg	Pain Threshold (NFR)
Schestatsky et al. (2007)	9	5.40	17.1 (NS)	OFF ON	NS but inc. L-DOPA	9	Heat Laser	Hand	Sensory Threshold Pain Threshold
Schestatsky et al. (2007)	9	6.00	19.1 (NS)	OFF ON	NS but inc. L-DOPA	9 <sup>a</sup>	Heat Laser	Hand	Sensory Threshold Pain Threshold
Vela et al. (2007)	25	11.38	24.6 (ON)	ON	NS	25	Pressure ( <i>algometer</i> )	Hand	Pain Threshold
Vela et al. (2007)	25	4.72	19.9 (ON)	ON	NS	25 <sup>a</sup>	Pressure ( <i>algometer</i> )	Hand	Pain Threshold
Brefel-Courbon et al. (2005)	9	9.60	25.0 (OFF) 15.0 (ON)	OFF ON	Mixed (L-DOPA and/or DA agonists)	9	Cold pressor	Hand	Pain Threshold
Djaldetti et al. (2004)	51	5.30	24.0 (OFF)	OFF	Mixed (L-DOPA and/or DA agonists)	28	Heat	Hand	Pain Threshold
Massetani et al. (1989)	15	4.10	NA	ON	Mixed (L-DOPA with or without peripheral decarboxylase inhibitor = 10, drug free = 5)	8	Electrical	Face	Sensory Threshold Pain Threshold Pain Threshold (blink reflex)
<b>TOTAL</b> 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	Hand = 13; Forearm = 10; Leg = 10; Face = 2; Foot = 2; Neck/Head/Upper Arm = 1	Pain Threshold = 21; Sensory Threshold = 9; Intensity = 7; Suprathreshold (moderate pain/tolerance) = 6; Unpleasantness = 1

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

<sup>a</sup> Same control group used for '-a' and '-b' studies.

<sup>b</sup> Estimated from MDS-UPDRS-III score of 33.8 using conversion formula (Goetz et al., 2012).

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 (Tipton, 2015), 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 (Fisher and Tipton, 2014).

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  $I^2$  (Higgins et al., 2003), 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 (Cury et al., 2016). Conversely, the methods of constant stimuli/adjustment (where constant temperatures are gradually adjusted) (see Yarnitsky and Pud, 2004) 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 (Fil et al., 2013). 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 (Egger et al., 1997) with  $p < 0.05$  indicating asymmetry. If present, a revised effect size assuming the presence of publication bias was computed using the trim and fill method (Duval and Tweedie, 2000).

As the citation refers to a package (robumeta) within a computer program (R): all analyses were performed using the *robumeta* package (Fisher and Tipton, 2014) in R (R Core Team, 2014).

## 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 (Fig. 1).

### 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 (Fahn and Elton, 1987) 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 (Tan et al., 2015), 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  $\geq 25$  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.

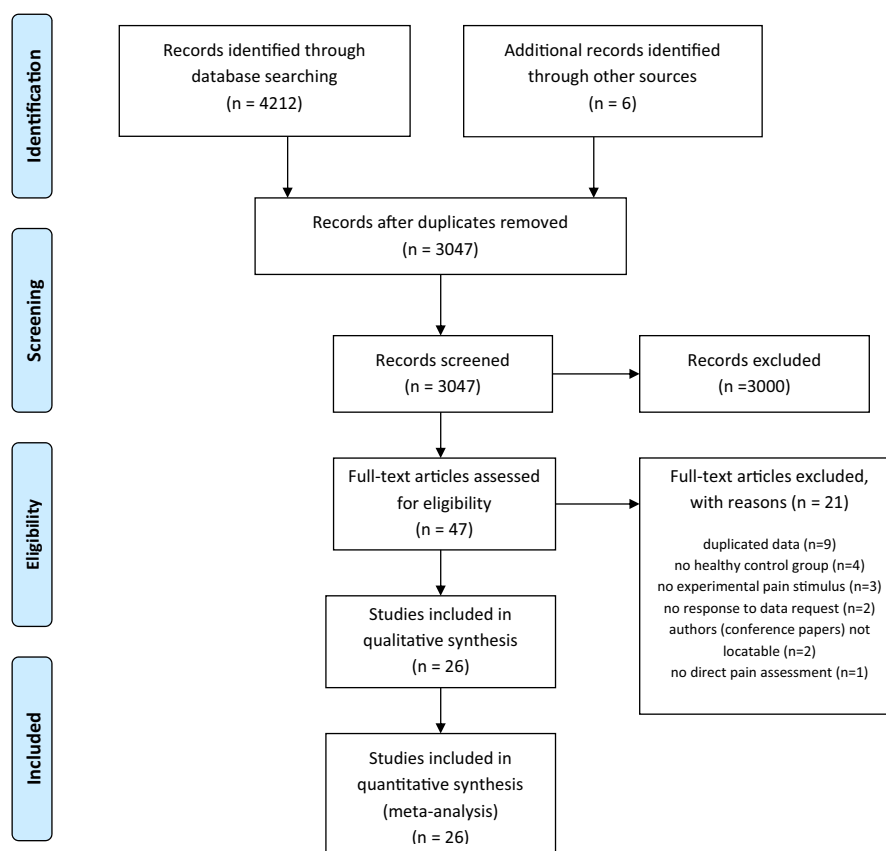


Fig. 1. PRISMA flow diagram.

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 (Tan et al., 2015), OFF states were achieved by the withdrawal of dopaminergic medication, with pain testing usually taking place after a  $\geq 12$ -h 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 (Gwet, 2002) 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 ( $<24$  h) 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 (Nolano et al., 2008) reported implausible pain thresholds ( $9.1$ – $12.4^\circ\text{C}$ ) for heat stimulation (values for other stimuli were plausible), and a further study (Schestatsky et al., 2007) reported means and SDs for pain threshold highly inconsistent with reported  $p$ -values (even when SDs were treated as SEMs), and so this specific data were excluded.

#### 3.5. Meta-analysis results

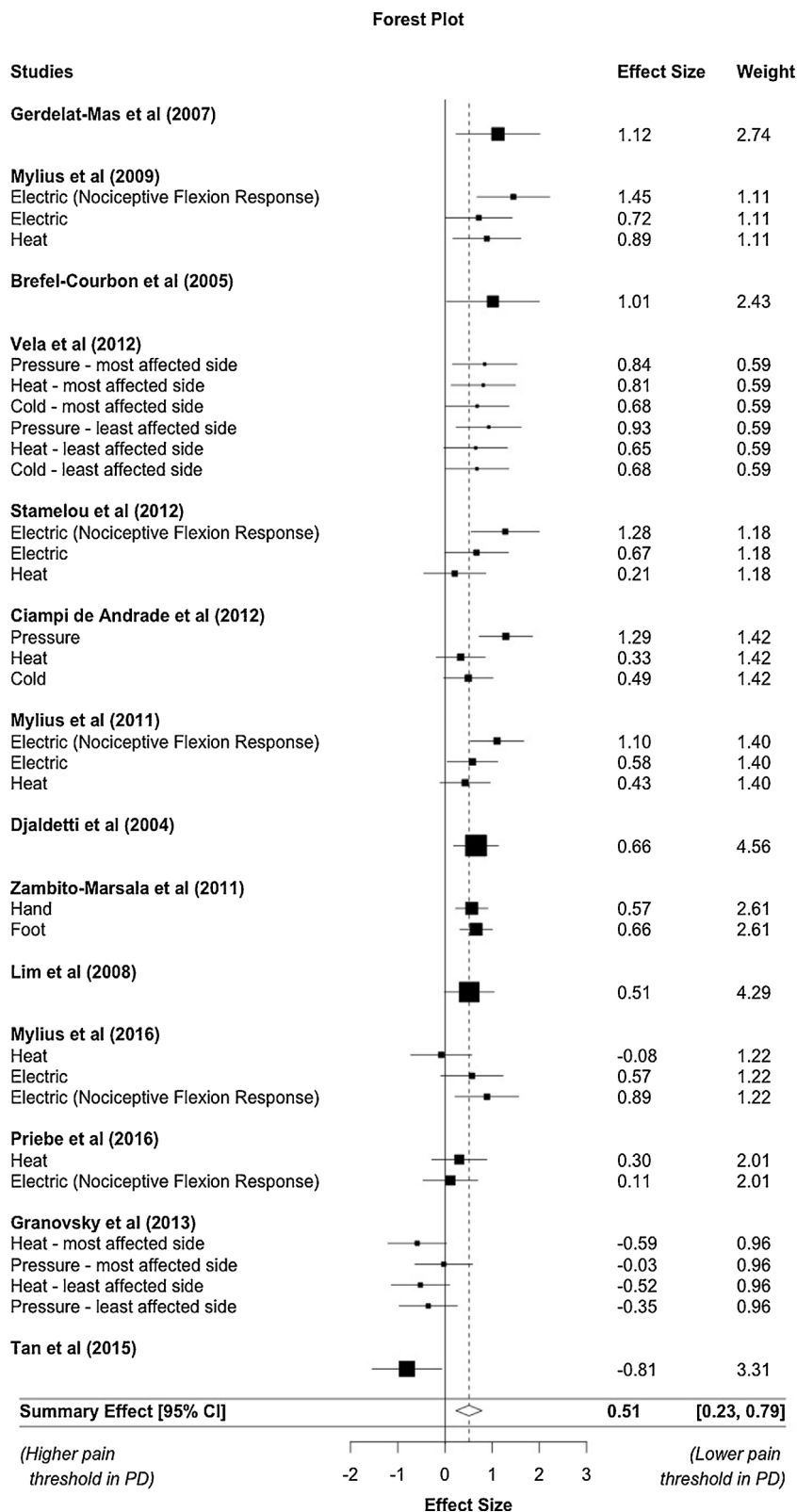
##### 3.5.1. Pain threshold

Pain threshold data was examined for  $k=20$  studies comprising a total sample of  $N=926$  ( $n=577$  PD,  $n=473$  HCs), with PD patients 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 ( $SMD=0.37$ ,  $CI_{95}[0.16, 0.57]$ ,  $p=0.001$ ). 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 ( $k=14$ ;  $SMD=0.51$ ,  $CI_{95}[0.23, 0.79]$ ,  $p=0.002$ ), along with moderate-high heterogeneity ( $I^2=64\%$ ). For ON state data, lower overall pain threshold in PD





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

was also found but with a reduced effect size ( $k = 13$ ;  $SMD = 0.23$ ,  $CI_{95}[0.02, 0.45]$ ,  $p = 0.04$ ) and moderate heterogeneity ( $I^2 = 49\%$ ). A forest plot of pain threshold data for the OFF state is provided in Fig. 2.

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:  $z = 0.30$ ,  $p = 0.76$ ; ON:  $z = 0.42$ ,  $p = 0.67$ ), 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 maximise 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 ( $SMD=0.30$ ,  $CI_{95}[-0.01, 0.61]$ ,  $p=0.06$ ). Analysis of different functional states indicated lower tolerance to suprathreshold pain during OFF ( $k=4$ ;  $SMD=0.44$ ,  $p=0.04$ ) states but not during ON ( $k=5$ ;  $SMD=0.15$ ,  $p=0.28$ ) states. For analysis of OFF state data, population confidence intervals (and thus  $p$ -values) may be wider or narrower (Tipton, 2015) 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),  $z=1.90$ ,  $p=0.054$ . A revised estimate using trim and fill methods suggested a slightly larger effect size ( $SMD=0.36$ ,  $p=0.01$ ) 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 (Tipton, 2015) 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 ( $k=19$ ;  $B=0.035$ ,  $p=0.24$ ) or UPDRS-III symptom severity ( $k=19$ ;  $B=0.006$ ,  $p=0.71$ ).

Results also indicated that effect size was significantly larger ( $k=19$ ;  $\Delta SMD=0.33$ ,  $CI_{95}[0.02, 0.64]$ ,  $p=0.039$ ) for OFF ( $B=0.58$ ) than ON ( $B=0.25$ ) states. This pattern of results was reproduced ( $k=19$ ;  $\Delta SMD=0.33$ ,  $CI_{95}[0.02, 0.66]$ ,  $p=0.041$ ), 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 ( $k=18$ ;  $\Delta SMD=0.34$ ,  $p=0.061$ ).

### 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 ( $k=20$ ;  $p=0.38$ ), mean study age ( $k=20$ ;  $p=0.62$ ), affected vs. non-affected side tested ( $k=9$ ;  $p=0.91$ ), anatomic site tested ( $k=17$ ;  $p=0.43$ ) or diagnostic criteria provided ( $k=20$ ;  $p=0.55$ ). For stimulus modality ( $k=20$ ), however, PD patients demonstrated lower pain threshold than HCs in response to cold ( $SMD=0.62$ ,  $p=0.011$ ), electrical ( $SMD=0.53$ ,  $p<0.001$ ) and pressure ( $SMD=0.41$ ,  $p=0.055$ ) stimuli, but not heat stimuli ( $SMD=-0.05$ ,  $p=0.79$ ). PD-related pain could not be reliably assessed as a moderator, as the adjusted  $df$  was  $< 4$  (Tipton, 2015).

### 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 ( $p=0.79$ ) or control selection ( $p=0.68$ ) 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 ( $\Delta SMD=0.40$ ,  $p=0.052$ ).

### 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 ( $k=7$ ;  $\Delta SMD=-0.25$ ,  $CI_{95}[-0.11, -0.38]$ ,  $p=0.004$ ). 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 ( $k=5$ ;  $\Delta SMD=-0.22$ ,  $p=0.045$ ). 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 (Cohen, 1988), 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 ( $p=0.052$ – $0.061$ ).

#### 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

(Fil et al., 2013; Jarcho et al., 2012). 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 (Fil et al., 2013). 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 (Cury et al., 2016), the diminished pain response seen in schizophrenia (Stubbs et al., 2015) a disorder linked to aberrant dopaminergic neurotransmission, and evidence from animal models suggesting a role of dopamine in chronic regional pain syndrome (Wood, 2008). 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 (Jarcho et al., 2012; Wood, 2008). Furthermore, if the suggestion that the underuse of conventional painkillers in PD patients is attributable to poor efficacy in this group (Perez-Lloret et al., 2012), 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 serotonergic) 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 normalisation

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 (Nolano et al., 2008) 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 (Valkovic et al., 2015), 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 (Cury et al., 2016), 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 (Folstein et al., 1975).

#### 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 (Staahl et al., 2009). 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.

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#### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.arr.2017.01.005>.

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