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

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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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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 (Schrag 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)