Experimental Gerontology 82 (2016) 30–38

Contents lists available at ScienceDirect

Experimental Gerontology

journal homepage: www.elsevier.com/locate/expgero

Review

Is pain sensitivity altered in people with Alzheimer's disease? A systematic review and meta-analysis of experimental pain research

Brendon Stubbs [a,b,*], Trevor Thompson [c], Marco Solmi [d,i], Davy Vancampfort [e,f], Giuseppe Sergi [g], Claudio Luchini [h], Nicola Veronese [g,i]

[a] Physiotherapy Department, South London and Maudsley NHS Foundation Trust, London SE5 8AZ, UK
[b] Health Service and Population Research Department, Institute of Psychiatry, King's College London, De Crespigny Park, London SE5 8AF, UK
[c] Faculty of Education and Health, University of Greenwich, London SE9 2UG, UK
[d] Department of Neurosciences, University of Padova, Padova, Italy
[e] University Psychiatric Centre, KU Leuven, KU Leuven Departement of Neurosciences, Leuvensesteenweg 517, B-3070 Kortenberg, Belgium
[f] KU Leuven Department of Rehabilitation Sciences, Tervuursevest 101, B-3001 Leuven, Belgium
[g] Department of Medicine (DIMED), Geriatrics Division, University of Padova, Italy
[h] Department of Pathology and Diagnostics, University and Hospital Trust of Verona, Verona, Italy
[i] Institute of Clinical Research and Education in Medicine (IREM), Padova, Italy

ARTICLE INFO

Article history:
Received 14 March 2016
Received in revised form 19 May 2016
Accepted 30 May 2016
Available online 2 June 2016

Section Editor: Christian Humpel

Keywords:
Alzheimer's disease
Dementia pain
Experimental pain
Meta-analysis
Systematic review

ABSTRACT

Background: Clinical studies suggest people with Alzheimer's disease (AD) have altered pain sensitivity. Experimental pain research is equivocal.
Objective: Conduct a meta-analysis to investigate if people with AD have altered pain sensitivity compared to healthy controls (HCs).
Methods: Three authors searched electronic databases from inception till November 2015 for experimental pain studies in AD vs. HCs. Outcome measures were pain threshold, tolerance, pain ratings, heart rate response to noxious stimuli and the Facial Action Coding System (FACS). Random effect meta-analysis calculating Hedges' g ± 95% confidence intervals (CI) was conducted.
Results: Thirteen studies were identified, including 256 people with AD (74.6 (±5.6) years, 59% females with a mean mini mental state examination (MMSE) score of 19.2) and 260 HCs. Meta-analysis demonstrated no significant difference in pain threshold ($g = 0.025$, 95% CI −0.315-0.363, $p = 0.88$, n AD = 135, n HCs = 157), pain tolerance ($g = -0.363$, 95% CI −2.035-1.309, $p = 0.67$, n AD = 41, n HCs = 53) or pain intensity ratings ($g = 0.03$, $p = 0.89$, n AD = 138, n HCs = 135). Heart rate response to pain was less pronounced in AD but not significant ($g = -0.746$, $p = 0.11$). People with AD (n = 90) had significantly higher FACS scores versus HCs (n = 109) ($g = 0.442$, $p = 0.03$) indicating increased pain. Meta-regression demonstrated that an increasing percentage of AD female participants moderated pain threshold ($p = 0.02$) whilst MMSE scores did not ($p = 0.19$).
Conclusion: People with AD have a greater sensitivity to pain when validated observer ratings of facial expressions are used. Verbal response to painful stimuli, even under experimental conditions, may mean pain is not identified in people with AD. Clinically useful observer rated pain tools may be the most appropriate way to assess pain in AD.

Contents

* Corresponding author at: Physiotherapy Department, South London and Maudsley NHS Foundation Trust, Denmark Hill, London, UK.
E-mail addresses: brendonstubbs@kcl.ac.uk, brendon.stubbs@kcl.ac.uk (B. Stubbs), t.thompson@gre.ac.uk (T. Thompson), marco.solmi83@gmail.com (M. Solmi), Davy.Vancampfort@upckuleuven.be (D. Vancampfort), giuseppe.sergi@unipd.it (G. Sergi), claudio.luchini@katamail.com (C. Luchini), ilmannato@gmail.com (N. Veronese).

http://dx.doi.org/10.1016/j.exger.2016.05.016
0531-5565/

1. Introduction

There is an increasing emphasis on the timely identification and management of pain among people with dementia, with prevalence estimates ranging between 50 and 93% (Corbett et al., 2014; Abdulla et al., 2013; van Kooten et al., 2015). Alzheimer's disease (AD) is the most common form of dementia, accounting for approximately 60% of cases (Lobo et al., 2000). In addition to changes in the transentorhinal cortex and hippocampus regions that occur with AD (Nelson et al., 2009), neurodegenerative changes in the medial thalamic nuclei, hypothalamus, cingulate and insular cortex have been identified (Cole et al., 2006). These areas are key components of the medial pain system, which is integral to the processing of the affective-motivational dimension of pain (Jones et al., 2003; Scherder et al., 2003). Interestingly, the areas of the brain that comprise the lateral pain system, which are related to the sensory-discriminative dimension (location, sensory quality and intensity) of pain appear to be relatively unaffected in AD (Cole et al., 2006). Collectively, these findings suggest that the way pain is appraised as well as the emotional component of pain (e.g. distress) may be particularly affected in AD. Moreover, people with AD experience considerable deteriorations in their cognitive ability, making the identification and communication of pain for the individuals affected and healthcare staff challenging (Corbett et al., 2012).

These inherent challenges of accurately assessing the prevalence of pain among people with AD, may mean that current prevalence rates are greatly underestimated (Corbett et al., 2012). Nonetheless, it is essential that pain is identified and appropriately managed among people with dementia, since undetected pain has been associated with functional decline (Sampson et al., 2015), falls (Stubbs et al., 2014) and greater behavioural and psychiatric symptoms of dementia (BPSD) such as agitation (Husebo et al., 2011; Pieper et al., 2013). Despite the fact that people with dementia seem to have a higher prevalence of pain than matched healthy controls (HCs), some evidence suggests that pain is undertreated in this group (Hunt et al., 2015; Hoffmann et al., 2014). However, a recent study among nursing home residents has suggested this may not be the case (Jensen-Dahm et al., 2015a).

Understanding if pain sensitivity is altered in AD is important to inform the clinical assessment and management of pain in this group. Experimental pain testing methods circumvent some of the concerns attributed with pain data collected among people with AD in clinical settings. Noxious stimulation can be precisely controlled, and the laboratory setting facilitates the assessment of pain using observer ratings or self-report ratings and stimulus-dependent or physiological measures including pain threshold, pain tolerance and heart rate response. Given that some of these measures rely more heavily on verbal communication and intact cognitive processing than others, it is important to consider a range of assessment measures when examining pain sensitivity in AD, given that this type of impairment is an important feature of the condition (Beach et al., 2015a).

A previous narrative review (Defrin et al., 2015) of the experimental pain literature in AD concluded that the research is equivocal but proposed that pain sensitivity does not appear to be reduced in AD versus HCs. Whilst this narrative review, conducted by experts in the field, was helpful and advanced the field, some pertinent questions remain unanswered. For instance, no meta-analysis has been undertaken, a technique which enables the logical pooling of studies which can provide a more accurate oversight of any outcome as opposed to considering individual studies in isolation (Ioannidis, 2009). In addition, it remains unclear how the pain experience of people with AD is influenced by different assessment methods, dimensions and patient characteristics (e.g. age, gender and cognition). Meta-regression can help disentangle the influence of important moderators.

The aim of the current paper was to conduct a comprehensive systematic review and meta-analysis comparing AD and HCs participant's response to experimentally induced pain. Specific aims are to: (1) examine whether AD and HCs differ in sensitivity to experimentally-induced pain; (2) examine whether pain sensitivity is altered according to the method of pain assessment, including pain threshold, pain tolerance, self-reported pain ratings, physiological response to painful stimuli and the observer rated Facial Action Coding System (FACS, (Prkachin, 1992)); (3) conduct meta-regression investigating the influence of potentially important moderating variables (e.g. age, cognitive status).

2. Method

This systematic review was conducted in accordance with the MOOSE guidelines (Stroup et al., 2000) and the PRISMA statement (Moher et al., 2009).

2.1. Eligibility criteria

Studies were selected for inclusion that utilised: (1) A group with AD, diagnosed according to recognized clinical assessments (e.g. DSM, ICD) and meeting the NINCDS-ADRDA Alzheimer's Criteria (McKhann et al., 2011); (2) a comparison control group of healthy individuals without any known cognitive impairment; (3) An experimental pain stimulus and at least one of the following established pain response measures: pain threshold, pain tolerance, pain ratings, physiological response to painful stimuli (e.g. heart rate changes) and observer-rated facial assessments of pain response (e.g. FACS).