Pain, aging and dementia: Towards a biopsychosocial model

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Abstract

Dementia is a progressive disease associated with irreversible impairment and loss of cognitive abilities. About half of older people with dementia experience pain. In this paper, we propose that pain in older people with dementia can be conceptualized as the final result of the interaction of three heterogeneous phenomena, pain, aging, and dementia, which are created and influenced by the interactions of predisposing, lifelong, and current biopsychosocial factors. We review pain assessment in people with dementia using both self-report and observational/behavioral measures. We then review the biological/sensory, psychological (cognitive and affective) and social dimensions of pain in dementia. The available data suggest that dementia does not impact pain threshold or tolerance. To date, there is little research on the social dimension of pain in dementia. Changes in the affective domain in response to experimental pain have been contradictory with evidence supporting both increased and decreased unpleasantness and emotional responsiveness in people with dementia compared to healthy controls. Clinically, depression is a significant burden for older people with dementia and chronic pain. The relationship between pain and other neuropsychiatric symptoms is controversial, and there is insufficient evidence on which to base conclusions. Some of the most important dementia-related changes may arise in the cognitive domain, including impairments of semantic and episodic memory for pain, executive function, and pain anticipation. Changes in brain activation and interconnectivity support many of these conclusions. Despite methodological limitations, we conclude there are compelling preliminary data to support a biopsychosocial framework of pain and dementia. Future research directions, especially the need for improved assessment tools, are highlighted.

Keywords: pain, aging, dementia, biopsychosocial model

1. Introduction

Dementia is a progressive disease associated with irreversible impairment and loss of cognitive abilities (Prince et al., 2013). Approximately 4.5-8% of people over seventy and 15-64% of people over eighty will experience dementia (Prince et al., 2013). As the population ages, the number of older people who experience dementia will also increase (Prince et al., 2013). There are several types of dementia but differentiating them is beyond the scope of the present review [For a review of this topic, please see Scott and Barrett (2007)].

In the early 1990s, Markinski (1991) and Hurley et al (1992) were among the first to propose that discomfort, including pain, in people with dementia should be a focus of clinical and research attention. At that time, little was known about how pain and dementia impacted each other or even whether people with dementia continued to experience pain.

We now know pain persists in dementia. Although there are wide ranging prevalence estimates, a recent systematic review concluded 46 – 56% of older people with dementia experience pain (van Kooten et al., 2016). Its prevalence does not appear to differ among dementia subtypes: Alzheimer's Disease (AD, 45.8%; 95% CI: 33.4-58.5), vascular dementia (56.2%; 95% CI: 47.7-64.4) and mixed AD and vascular dementia (53.9%; 95% CI: 37.4-70.1). These rates are comparable to estimates based on community-living cognitively intact older people (Shega et al., 2010). Within the same care settings, pain may be more (Bjork et al., 2016), less (Tan et al., 2015) and equally common (Lövheim et al., 2006) in those with dementia compared to those without dementia. We conclude, until further evidence is available, that the prevalence of pain among older people with dementia is comparable to other groups of older people.

It has been suggested that older people with dementia are at greater risk than those who are cognitively intact for inadequate pain management (McDermott et al., 2014; Monroe et al., 2012). For

instance, a recent meta-analysis found nursing home residents with dementia receive fewer analgesics than residents who are cognitively intact, despite comparable numbers of diagnosed painful conditions (Tan et al., 2015). However, other reviews and empirical studies have found older people with dementia use more paracetamol (Corbett et al., 2014) and opioids (Jensen-Dahm et al., 2015a) than those without dementia. At present, it is not clear whether pain is undertreated in older people with dementia compared to older people who are cognitively intact. Careful analyses that simultaneously consider ability to report pain, the nature of potentially painful conditions, and the type and dosage of analgesics are needed.

2. Research in pain and dementia

As the subfield of pain and aging emerged, attention to older people with dementia grew (Gagliese, 2009). Clinically, much of the research focused on the development of behavioral observation scales. This work led to a plethora of assessment tools, none especially better than the others. Another stream of research focused on the documentation and management of pain in people with dementia in various care and residential settings. In parallel, there has been research into pain sensitivity and the impact of the neuropathology of dementia on the neurobiology of pain. Unfortunately, the evidence across these research streams has rarely been considered conjointly. Although data on experimental pain cannot be directly generalized to clinical pain (Gagliese, 2007), such an integration may be critical to advance this subfield of pain research towards a full biopsychosocial model of pain and aging (Gagliese, 2009). In this paper, we examine evidence for a biopsychosocial model of pain in dementia.

2.1 Pain, aging and dementia: the interaction of three biopsychosocial phenomena

Since Melzack and Wall's (1965) gate control theory, pain increasingly has been understood as a multidimensional experience made up of sensory, cognitive, and affective components. Central to this

theory is the idea that the brain plays the key role in the creation and modulation of pain across these

dimensions. Preclinical neurobiological and human imaging studies have supported and refined these

theoretical conceptualizations, and we are quickly growing in our understanding of the widespread

neuromatrix which creates the experience of pain (Melzack, 1999; Melzack and Katz, 2013). The

biopsychosocial model of pain is an extension of Melzack and Wall's theoretical and empirical work.

Although it is beyond the scope of this paper to review the abundant evidence supporting this model

(please see Gatchel et al. (2007) for a comprehensive review), there is widespread agreement that

chronic pain is influenced by a broad range of predisposing, lifelong and current biological,

psychological and social risk and protective factors.

Age is one of the many factors that plays a role in pain (Gagliese and Melzack, 2013). Although

this applies across the lifespan, in this paper we will focus only on older people. Like pain, aging is a

biopsychosocial phenomenon comprising nonuniform, nonlinear and heterogeneous changes across

biological, psychological and social systems which are influenced by myriad predisposing, lifelong, and

current factors (Cassel, 2003). The need for a biopsychosocial framework of pain and aging, which

includes cognitive function, has been recognized (Dunn, 2010; Gagliese, 2009).

One of the first biopsychosocial frameworks of dementia was proposed by Cohen-Mansfield

(Cohen-Mansfield, 2000). Consistent with approaches to pain and aging (Dunn, 2010; Gagliese, 2009) ,

its core assumption is that a person's current manifestation of dementia is the net result of a broad range

of predisposing, lifelong, and current biological, psychological, and environmental factors. These

factors interact and impact on cognition, behavior, functional status, and affect. Importantly, Cohen-

Mansfield proposes that pain is among the current psychosocial and medical conditions which can

impact on cognition, behavior, and affect. Although not stated explicitly, we believe Cohen-Mansfield

would agree, given her pioneering work in pain and dementia, that pain is also a current condition

impacting functional status. Therefore, according to this framework, pain impacts on current

presentation of dementia. The reciprocal relationship, that is, the impact of dementia on pain, is not

considered.

Spector and Orrell (2010) recently updated and extended Cohen-Mansfield's model. Their

primary contribution was to add a trajectory ranging from normal aging, to mild cognitive impairment,

to dementia and then to death. Their other substantive contribution was to explicitly categorize

biopsychosocial factors as either fixed (not amenable to change, e.g., age) or tractable (may be amenable

to change e.g., mood). It is the interaction of fixed and tractable factors that influences the onset,

symptom profile, and progression of dementia. Finally, they propose the impact of biopsychosocial

factors varies along the trajectory from normal aging to death. That is, the same factors may have

different effects depending on cognitive status. This fits well with the emerging evidence that some

factors may have different effects on pain depending on age and life-stage (Dunn, 2010; Gagliese,

2009). Spector and Orrell include pain in the model as one of the consequences of physical illness that

may impact mood and motivation. Like Cohen-Mansfield (2000), this model does not consider the

impact of dementia on pain. To our knowledge, a model of these reciprocal relationships is not yet

available.

Taken together, pain in older people with dementia can be conceptualized as the final result of

the interaction of three heterogeneous phenomena - pain, aging, and dementia - which are created and

influenced by the interactions of predisposing, lifelong, and current biopsychosocial factors. There is

considerable overlap in the factors which may play roles, with the brain, including neuropathology

(Scherder et al., 2003), playing the key role. We posit that pain, aging, and dementia have reciprocal

relationships with each other. The complexity of the interactions amongst these three phenomena across

their unique and shared biopsychosocial influences and over time is apparent.

In this paper, we integrate the biopsychosocial model of dementia (Spector and Orrell, 2010) with the biopsychosocial model of pain (Gatchel et al., 2007; Melzack and Katz, 2013) and the model of observer judgments of pain (Prkachin et al., 2007) (See Figure 1). Of necessity, we are unable to review every factor which has been studied and instead focus on recent research, with priority given to systematic reviews and well-established findings. We review the biological/sensory, psychological (cognitive and affective) and social dimensions of pain in dementia (Figure 1) acknowledging that this division of factors into dimensions is artificial as all pain is the final interaction of these three dimensions (Melzack, 2011). We ask whether and how pain and dementia impact on each other. Admittedly, this question is premature. There are significant gaps, contradictions, and limitations to the research. Therefore, the review and model, of necessity, are tentative and offered not as a comprehensive framework but as a snapshot of our current knowledge and as a guide to future research.
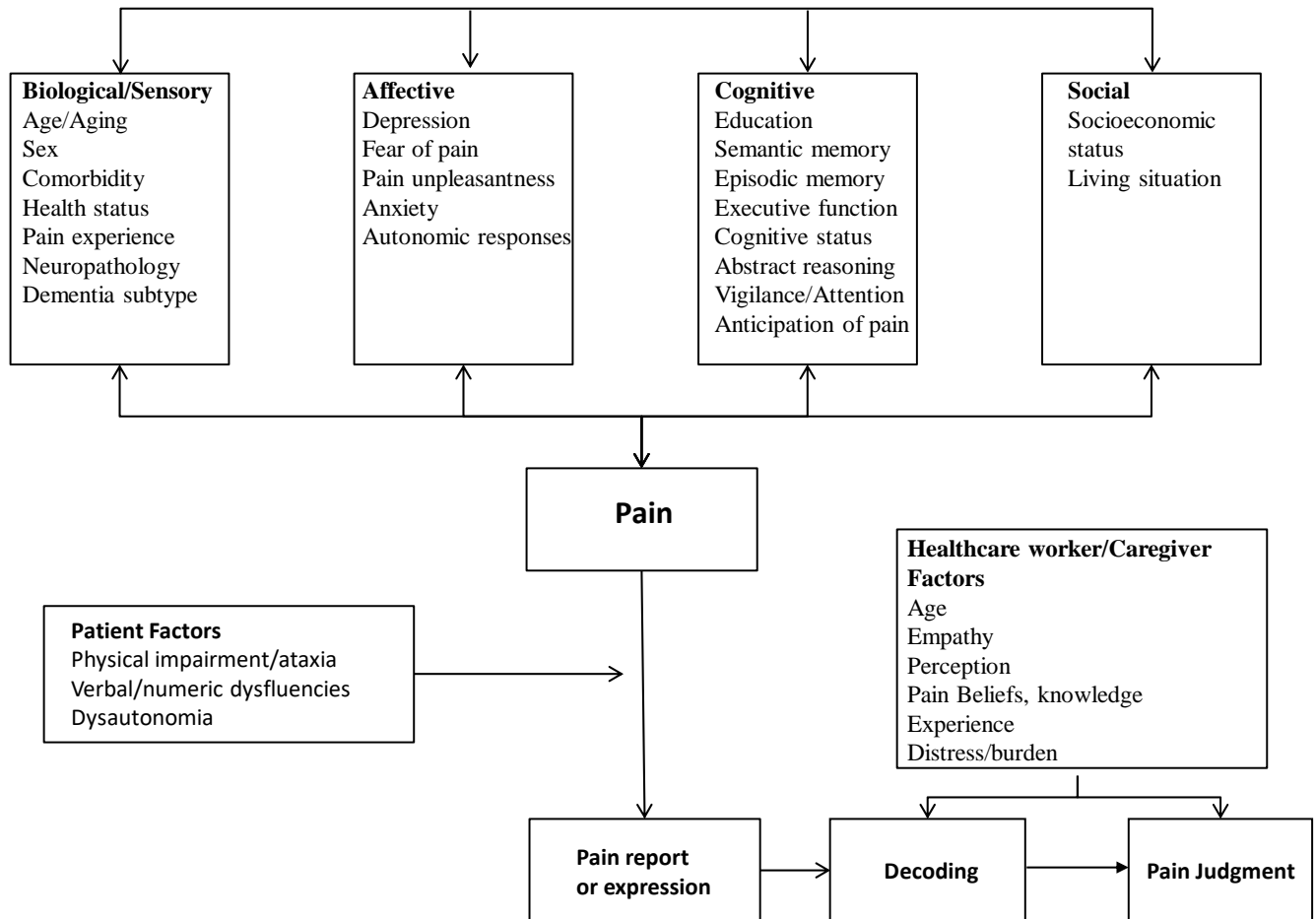
Biological/Sensory
Age/Aging
Sex
Comorbidity
Health status
Pain experience
Neuropathology
Dementia subtype

Affective
Depression
Fear of pain
Pain unpleasantness
Anxiety
Autonomic responses

Cognitive
Education
Semantic memory
Episodic memory
Executive function
Cognitive status
Abstract reasoning
Vigilance/Attention
Anticipation of pain

Social
Socioeconomic status
Living situation

Pain

Patient Factors
Physical impairment/ataxia
Verbal/numeric dysfluencies
Dysautonomia

Healthcare worker/Caregiver Factors
Age
Empathy
Perception
Pain Beliefs, knowledge
Experience
Distress/burden

Pain report or expression

Decoding

Pain Judgment

Figure 1. The biopsychosocial model of pain and dementia. Adapted from (Melzack and Katz, 2013; Prkachin et al., 2007; Spector and Orrell, 2010).

3. Pain measurement in people with dementia

We begin with the biggest challenge in this field: valid pain assessment. Despite the surge in research attention, we have yet to establish the best way to assess pain in older people with dementia. As such, it is necessary to consider the impact of dementia on pain expression, whether verbal or behavioral, independently of its impact on the actual experience of pain (see Figure 1).

3.1. Self-report of pain.

There has been a groundswell of research into pain assessment in people with dementia in the

last twenty-five years. One arm of this endeavor has focused on the use of self-report pain scales by

those with mild-to-moderate dementia and preserved ability to communicate verbally. These studies

have been mixed with some reporting that people with mild-to-moderate cognitive impairment are able

to reliably self-report their pain (Chen and Lin, 2015; Ngu et al., 2015; Pautex et al., 2005), and others

reporting that a sizable proportion are either unable to complete self-report measures or provide scores

that are so highly variable, even with very short inter-rating intervals, as to be random (Malara et al.,

2016; Pesonen et al., 2009; Wynne et al., 2000). While several studies have reported that all patients,

regardless of severity of cognitive impairment, were able to complete the assessment (Chen and Lin,

2015; Leong et al., 2006; Ngu et al., 2015), others report 27% - 64% were unable to complete these

scales (Closs et al., 2004; Cohen-Mansfield, 2008; Pesonen et al., 2009; Wynne et al., 2000). Difficulty

completing scales is associated with severity of dementia (Cohen-Mansfield, 2008). Other

characteristics of those who can and cannot complete self-report scales remain to be established.

It is not surprising that people with dementia have difficulty self-reporting their pain. Even the

simplest pain report, namely, indicating the presence or absence of pain, makes cognitive demands. The

person must be able to understand and remember the instructions of the task and have sufficiently

preserved semantic memory of the construct of pain and episodic memory of previous pain (Oosterman

et al., 2014). Perhaps more challenging, they must be able to attend to and interpret a subjective

experience as pain and then communicate that interpretation to a researcher or clinician. This may be

difficult in a novel (e.g., a pain lab) or medical setting which can destabilize the person with dementia,

potentially exacerbating neuropsychiatric and cognitive symptoms (Brown, 2011; Kales et al., 2015; Smith et al., 2006).

Rating pain intensity adds a layer of complexity. This task requires not only understanding the concept of pain and interpreting a subjective experience as pain, but also quantifying that subjective experience along a metric ranging from none to most intense. This would require sufficiently preserved numeracy (Numeric Ratings, Poker Chips), verbal fluency (Verbal Descriptor Scales), or facial expression interpretation (recognition, comparison and quantification), each of which can be compromised in dementia (Herr and Garand, 2011). All ratings of intensity, regardless of scale, require quantification along some dimension of intensity or unpleasantness which is anchored, often, by comparison with previous experience. There is evidence that within the same sample of older people with dementia, a larger proportion is able to indicate pain presence or absence than is able to provide pain intensity ratings (Oosterman et al., 2014). In addition, as the complexity and need for abstract quantification increases, such as the Visual Analog Scale (VAS), which requires the conversion of a subjective experience into a length of line, difficulties completing the scale also increase (Closs et al., 2004; Krulewitch et al., 2000; Pesonen et al., 2009). This is consistent with data from cognitively intact people showing increasing age is associated with increasing difficulty completing the VAS (Gagliese et al., 2005; Herr et al., 2004; Peters et al., 2007).

3.2 Observational measures of pain.

As dementia progresses, self-report becomes impossible, and it is necessary to rely on the observation of pain behaviors and facial expressions. At least twenty-eight observational pain assessment instruments have been developed for people with dementia (Flo et al., 2014; Lichtner et al., 2014). Consistent with the guidelines of the American Geriatrics Society, many assess facial expression,

vocalizations, body movements, and changes in interpersonal interactions, activity patterns or routines, and mental status (Bjoro and Herr, 2008; While and Jocelyn, 2009). Detailed description of these measures is beyond the scope of this article, but see Corbett et al. (2012). Importantly, recent reviews have concluded that most lack sufficient validation, that sensitivity to change after pain-relieving intervention is unclear, and that none can be strongly recommended over the others (Bjoro and Herr, 2008; Flo et al., 2014; Lichtner et al., 2014; While and Jocelyn, 2009).

A recognized challenge to the specificity of these scales is the difficulty of disentangling behavioral manifestations of pain from those of dementia (American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older Persons, 2009). This may lead to both pain over- and under-estimation. An additional, less often considered, challenge of these scales arises from the interpersonal nature of the task. Observers are required to decode the behaviors and facial expressions of people with dementia (Figure 1). It is well known that there are often discrepancies between self and proxy pain reports when self-reports are possible (Prkachin et al., 2007), including reports made by people with dementia and their caregivers (Barry et al., 2015; Hunt et al., 2015). Of course, it is not possible to assess concordance when one member of the dyad is incapable of verbal self-report. There is evidence that pain judgments are influenced by a range of observer and target factors. When observing older people, pain judgments may be influenced by observers' age, empathy, pain beliefs, and professional experience and by the targets' cognitive status, age, and gender (Green et al., 2009; Lautenbacher et al., 2013; Prkachin et al., 2001; Robinson and Wise, 2003; Weiner et al., 1999). Specifically, being older, female, and cognitively impaired is associated with greater observer pain judgments (Lautenbacher et al., 2013). These types of biases are important components of the social dimension of pain (Hadjistavropoulos and Craig, 2002), and they may undermine the validity and

reliability of observational measures of pain if researchers are not careful to control them as potential confounders (Zwakhalen et al., 2006).

Taken together, it appears the symptoms of dementia, including impaired pain-related memory and cognition, behavioral or phenotypic overlap of dementia symptoms with pain, and biases in the interpretation of nonverbal pain cues likely impact self-report and observational measures of pain independent of the actual experience of pain. As a result, we have separated the experience of pain from pain reporting and expression in the model (Figure 1). This should not be taken to suggest that inability to verbally or behaviorally express pain means pain is not experienced (Craig et al., 2002; Melzack, 1999). It means rather that we must be cautious in our interpretation of findings based on the currently available pain tools, and it highlights the urgent need for innovative assessment strategies that accommodate the unique cognitive and behavioral profiles of this group.

4. The Biological/Sensory Dimension of Pain

Bearing in mind the caveats regarding assessment, we turn now to the research into pain and dementia and consider whether dementia impacts pain. In the biological/sensory domain, research has focused on dementia-related patterns in sensitivity to experimental and clinical pain. There has been little research into underlying mechanisms. Studies comparing sensitivity to experimentally applied painful stimulation between those with mild-to-moderate dementia and healthy controls are available. In these paradigms, the stimulation and response parameters are well-controlled, and research participants attend to the stimulation and indicate when it first becomes painful [pain threshold, lowest level of stimuli perceived as painful (Melzack and Wall, 1988)] or when they wish it to cease [tolerance, or the greatest stimulation a person is willing to accept (Melzack and Wall, 1988)]. Therefore, completion of these assessments requires focused attention, semantic and episodic memory for pain, ability to decide whether or not a stimulus is painful, and then to report this and the desire for it to stop.

Many studies using these tasks report that participants were screened for ability to understand and complete the protocols in a meaningful way but few report how many potential participants were excluded for this reason [for example Monroe et al. (2016)]. This information is vital to understand the representativeness of the sample and the generalizability of the results. There are preliminary data to suggest that for a variety of experimental pain protocols, people with mild-to-moderate Alzheimer's Disease (AD) are able to understand and complete the task and show similar reliability and response bias as older cognitively intact people (Jensen-Dahm et al., 2014). Interestingly, for several of these parameters, reliability across testing sessions was only moderate in those with and without dementia. Unfortunately, Jensen-Dahm et al. (2014) do not describe the steps taken to assess understanding of the testing.

A recent systematic review with meta-analysis concluded pain sensitivity does not differ between older people with and without AD (Stubbs et al., 2016). Specifically, pain threshold for a variety of stimulation modalities is the same in both groups. Similarly, pain tolerance, although not studied as frequently as threshold, does not differ between the groups. Finally, intensity ratings provided in response to various modalities and types of stimulation also does not differ. Unfortunately, it was not possible to assess the roles of dementia severity or subtype or stimulation modality on these results. While the findings of similar pain thresholds, tolerances, test reliability and biases in cognitively intact and impaired older people support the validity of these protocols for assessing pain sensitivity in people with AD, replication with larger samples using a variety of test parameters is needed. Also, it is important not to lose sight of the findings of only moderate agreement between tests performed within a fairly short interval. Although this did not differ statistically from cognitively intact older people, it may nonetheless signal problems with reliability of the results in both groups.

It may not be possible to generalize these findings across dementia subtypes. For instance, although AD is associated with little change on most indices of pain sensitivity (Stubbs et al., 2016), frontotemporal dementia (FTD) has been associated with blunted pain sensitivity, including increased threshold and tolerance compared to cognitively intact controls (Carlino et al., 2010). Consistent with this, caregivers of people with FTD were more likely than caregivers of people with other types of dementia to report blunting or lack of awareness of pain (Bathgate et al., 2001). Although large-scale comparisons across different types of dementia are not currently available, it is important that future research no longer group heterogeneous patients into a "dementia" group, as this may obfuscate changes in pain.

There are emerging data comparing older people with and without dementia on pain habituation and sensitization paradigms. Jensen-Dahm et al. (2015b) applied four supra-threshold thermal stimuli to the arm of older people with and without mild-to-moderate dementia. Participants were asked to rate the intensity of each using a Coloured Visual Analog Scale. Both groups showed habituation, but it was slower in those with dementia. There was no evidence for increased sensitization. Jensen-Dahm et al. (2015b) speculate the difference in habituation rate may be secondary to changes in the affective-motivational dimension of pain, such as fear or anxiety, or to difficulties maintaining vigilance or remembering previous pain ratings or stimulation intensities.

In clinical and community samples, many older people with dementia report mild-to-moderate pain that interferes with daily activities (Breland et al., 2015; Hunt et al., 2015). Differences in the intensity of painful conditions across those with and without dementia or by dementia severity and type remain unclear (Hunt et al., 2015; Husebo et al., 2008; Scherder et al., 1999, 2015; Shega et al., 2010). Pain in people with dementia has been associated with greater comorbidities, including potentially painful diagnoses, female gender, lower education level, and greater impairment in activities of daily

living, psychological distress, and other neuropsychiatric symptoms (Breland et al., 2015; Hunt et al.,

2015; Jensen-Dahm et al., 2012). Although these findings support a biopsychosocial model,

methodological variation and limitations, especially challenges to pain assessment, necessitate caution in

drawing conclusions.

Taken together, the evidence from experimental, community, and clinical studies suggests that

changes to the sensory dimension of pain are subtle. Dementia does not appear to influence pain

threshold, tolerance or habituation. Prevalence of pain reports in the community do not vary

dramatically between people with and without dementia. Therefore, the sensory-discriminative

dimension of pain, including both peripheral and central mechanisms, may not be impaired in people

with mild-to-moderate dementia. This may be because the sensory cortex, at least in AD, remains

undamaged until dementia becomes severe (Defrin et al., 2015; Jensen-Dahm et al., 2015c). The

generalizability of these conclusions across dementia subtypes remains to be demonstrated.

5. The Psychological Dimension of Pain

5.1. The affective dimension of pain.

The psychological dimension of pain in dementia can be divided into affective and cognitive

dimensions. It has been proposed that the affective dimension of pain in AD may be impacted earlier

than the sensory dimension because limbic structures are affected earlier than the sensory cortex (Braak

and Braak, 1995; Scherder et al., 2003). In response to different modalities of painful stimulation, older

people with dementia report greater unpleasantness (Cole et al., 2006) and have greater pain-related

facial expressions than older cognitively intact people (Beach et al., 2016; Kunz et al., 2009; Scherder et

al., 2003; Stubbs et al., 2016). However, others have found that self-report ratings of pain

unpleasantness in response to mild-to-moderate levels of thermal pain do not differ between older

people with and without dementia and do not vary with severity of cognitive impairment (Monroe et al., 2017, 2016). Methodological differences make it difficult to reconcile these results.

Another approach to assessing the affective dimension of pain has involved measuring responses of the autonomic nervous system. Compared to cognitively intact people, those with moderate cognitive impairment show blunted autonomic responses, including galvanic skin response, heart rate and blood pressure, which may increase with the severity of the dementia (Beach et al., 2015; Plooij et al., 2011; Scherder and Plooij, 2012). At more intense stimulation levels, the autonomic responses of those with and without dementia may not differ (Rainero et al., 2000). It is difficult to know if these findings reflect changes in pain affect specifically or the well-known autonomic blunting associated with dementia more generally (Allan et al., 2007; Plooij et al., 2011), which has led some researchers to conclude that autonomic responsivity is not a reliable indicator of pain in dementia (Beach et al., 2015) or may only be reliable as a signal of severe pain (Plooij et al., 2011). Critically, autonomic responses, on their own, cannot be interpreted as pain nor should lack of autonomic response be interpreted as lack of pain (Plooij et al., 2011). How to reconcile the discrepant results from these different measures of the affective dimension of pain - inconsistent self-report, increased facial expression and decreased autonomic responding – is unknown at present.

In the clinical setting, the affective dimension of pain in people with dementia is often subsumed under the category of neuropsychiatric symptoms (NPS) which include delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy, disinhibition, irritability/lability, and aberrant motor, night-time, and/or eating behaviors (Guarnieri et al., 2012; Rosen et al., 2005; Torrisi et al., 2016; Zuidema et al., 2007). The nature of the relationship between NPS and pain is controversial with recent reviews coming to different conclusions (Flo et al., 2014; van Dalen-Kok et al., 2015). There is evidence that pain may trigger or exacerbate NPS and that pain management

may reduce them (Flo et al., 2014; Habiger et al., 2016). There may be some specificity to these effects, with pain management reducing restlessness and pacing but not hitting or kicking (Flo et al., 2014). This raises the possibility that only some NPS are pain-related. However, the prevalence of NPS among older people in long-term care settings may be as high as 90% (Bjork et al., 2016) and does not differ in residents with and without pain when measured using nonoverlapping behavioral indicators (Bjork et al., 2016). In addition, a recent meta-analysis did not support a relationship between pain and agitation (van Dalen-Kok et al., 2015). These findings call into question the usefulness of NPS as indicators of pain (van Dalen-Kok et al., 2015). With such high prevalence rates, the specificity of these symptoms for pain must necessarily be low, and their responsiveness to pain management may signal a nonspecific sedative effect of analgesics (Hayes et al., 2007) rather than pain relief per se. This is important because attributing NPS to pain may lead to overtreatment of pain and undertreatment of NPS. Conversely, attributing behavioral signs of pain to NPS may lead to undertreatment of pain and overtreatment of NPS. For example, the sedative effects of treatments for NPS may mask behavioral manifestations of pain (Kovach et al., 2001).

Despite this, NPS, especially agitation/aggression, are often items on observational pain scales with no guidance provided for differentiating behaviors associated with dementia from those related to pain (Corbett et al., 2014). This contributes to common method bias, the inflation of relationships between distinct constructs when they are measured in overlapping fashion (Flo et al., 2014). Unfortunately, research into pain, dementia and NPS is fraught with methodological limitations including not specifying how NPS are measured or using pain scales that confound pain with NPS (Flo et al., 2014; van Dalen-Kok et al., 2015).

There is stronger empirical support for a relationship between pain and depression in people with dementia. Both a narrative review (Flo et al., 2014) and meta-analysis (van Dalen-Kok et al., 2015)

found an elevated risk of depression in people with dementia and pain versus those without pain. In addition, an important longitudinal study, which followed people with dementia for two years, found self-reported pain intensity predicted subsequent caregiver reports of depression and decreased pleasant life events but not agitation (Snow et al., 2009). This study not only supports distinct relationships between pain and various NPS, it also illustrates the significant affective burden of pain in people with dementia. This burden may be comparable to that seen among older cognitively intact people with chronic pain (Flo et al., 2014).

Clearly, much more research is needed to study the affective dimension of pain in people with dementia. The results from experimental studies are difficult to reconcile, with evidence for increases, decreases and no change in the affective response to painful stimulation when comparing people with dementia to those who are cognitively intact. In clinical or long-term care settings, to date, there is little evidence to suggest that NPS are a specific sign of pain or that the affective domain of pain is significantly altered in those with dementia. This highlights the need for adequate assessment and management of both pain and depression in people with dementia. Interpreting depression in these patients as pain rather than depression may contribute to untreated distress as well as pain over-treatment (Breland et al., 2015).

5.2 The cognitive dimension of pain and dementia.

The cognitive dimension of pain is concerned with our understanding of pain, our beliefs and thoughts about it and the decisions we make about our symptoms, including coping attempts, treatment seeking and acceptance (Gatchel et al., 2007; Turk and Rudy, 1992). The cognitive dimension of pain in people with dementia has received some empirical attention, but large gaps remain. This is not surprising given the linguistic demands of most tools used to assess cognitive components of pain.

From a neuropsychological perspective, semantic and episodic memory of pain and the role of executive function have been examined. Oosterman et al. (2014) have recently shown that dementia is associated with impaired semantic memory of pain, including difficulties using pain descriptors and differentiating painful from nonpainful situations. Importantly, preserved semantic memory for pain is associated with ability to complete a facial pain rating scale. Although these data are preliminary, they serve as an important caveat to our interpretation of pain ratings made by people with dementia and suggest future studies must screen participants for sufficiently preserved semantic memory for pain, task comprehension, and completion at above chance levels.

It is important to consider the implications of impaired semantic and episodic memory for pain in people with dementia. Our understanding of the concept of pain, including its meaning, causes and potential consequences, often referred to as pain beliefs or pain attitudes, as well as our memories and previous experiences of pain play critical roles in the biopsychosocial model of pain (Gatchel et al., 2007). They fuel pain expectations, anxiety, catastrophizing, self-efficacy, coping, affective responses, symptom interpretation, treatment seeking and adherence, which have been associated with recovery from acute pain, transition to chronicity, and adjustment to chronic pain (Turk and Okifuji, 2002). In Melzack's neuromatrix theory, pain experience and learning shape the innate pain neuromatrix, thereby influencing every subsequent experience of pain (Melzack, 2005). As such, Oosterman et al's findings, although preliminary and requiring replication and expansion, may prove to be a cornerstone in the biopsychosocial approach to pain and dementia.

This is supported by studies that have carefully tracked autonomic reactivity in healthy controls and older people with dementia prior to, during and following potentially painful stimulation. In healthy controls and people with mild dementia, autonomic responses increase in anticipation of pain and then decrease after it. However, in those with more advanced dementia, autonomic responses are blunted

prior to the painful stimulation but are equal to or greater than those seen in healthy controls in response

to painful stimulation (Benedetti et al., 2004; Kunz et al., 2009; Plooij et al., 2011; Porter et al., 1996;

Rainero et al., 2000). Interestingly, heart rate changes after a warning of a painful stimulus and in

reaction to the actual painful stimulus were positively correlated with cognitive functioning (Benedetti et

al., 2004). That is, heart rate responses decrease with decreasing cognitive functioning. These findings

have been interpreted as a decline in anticipatory responses to pain. In other words, these results support

those of Oosterman et al. (2014): understanding the potential for experiences to be painful, an aspect of

the semantic memory of pain, is diminished in dementia. As such, the surprise of the pain, rather than its

intensity or unpleasantness, may better explain the enhanced facial expressions seen in people with

dementia in response to pain. This is a critical point. It suggests impairment in the cognitive dimension

of pain drives apparent changes in the affective dimension.

This anticipatory response, including preparation and monitoring as well as appraisal of coping

resources and selection of coping strategies, is also an aspect of executive function (Kunz et al., 2015).

Recently, Kunz et al. (2015) assessed the relationship between pain and a broad range of cognitive

capacities including executive function (abstract thinking and judgments), orientation, aphasia, apraxia,

memory, and information processing speed in a group of older people with mild-to-moderate dementia

of various types. Unfortunately, this study did not measure pain-specific memory. Responses to painful

electrical stimulation were measured using the nociceptive flexion reflex (NFR) and the facial action

coding system. They found executive functions are the best predictor of pain responsiveness, even after

controlling general cognitive status and memory. Specifically, impaired executive function is associated

with greater NFR and facial expression of pain. The authors propose that this reflects pathology of the

dorsolateral prefrontal cortex which may lead to loss of both executive function and pain inhibitory

systems. However, Scherder et al. (2008) found the opposite pattern. Namely, in older people with mild

dementia and chronic pain, impaired executive function is associated with lower self-reported pain intensity on the Coloured Visual Analog Scale and lower self-reported pain affect on the Faces Pain Scale. These authors speculate their results arise from prefrontal cortex pathology impairing executive function, pain, and recognition of facial expressions. It is difficult to reconcile these results as the studies use different measures of pain and executive function and different populations of people with dementia. Nonetheless, taken together, they suggest impaired executive function and semantic memory for pain impact not only pain self-report but also autonomic responsiveness, pain affect, and pain intensity. Although there are some inconsistencies in the literature and more research is needed to clarify the relationship between the full range of cognitive abilities and pain in people with dementia, it is plausible to conclude that the cognitive dimension of pain is impacted by dementia and that this may contribute to changes in the affective dimension of pain.

6. The Social Dimension of Pain and Dementia

Pain is also influenced by an array of social factors, including social support and the reactions of significant others to expressions of pain (Leonard et al., 2006; Mogil, 2015). Pain reports are communications that have impacts on both the person reporting the pain and the person receiving the report (Hadjistavropoulos et al., 2011; Mogil, 2015). Pain may be reported as a means of eliciting pain management, social support, empathy or as a way of distancing others or excusing behavior. The motivation and desired goals of a pain report are context specific.

The social dimension of pain in people with dementia has not received adequate empirical attention. However, it is interesting that most observational pain scales include social items such as withdrawal or change in usual social activity. It is important to remember that the impact of pain (i.e., withdrawal) does not equal pain and that these behaviors are in no way specific to pain. Therefore,

although the specificity of these items is questionable, they do recognize a social aspect to pain and its

impact.

There are few data considering pain and dementia at the relational level. In the experimental

setting, observer biases which may influence judgments about pain in people unable to give self-reports

have been identified (Figure 1). This may contribute to the discrepancies in pain reports between

caregivers and people with dementia who are capable of self-report. Caregivers are more likely than

people with dementia to report pain (Barry et al., 2015; Hunt et al., 2015; Jensen-Dahm et al., 2012).

Interestingly, reports were more likely to be discordant at mild-to-moderate than severe intensities,

suggesting an interaction with pain intensity (Jensen-Dahm et al., 2012). Perhaps biases operate more

strongly at lower levels of pain intensity when pain cues may be more difficult to interpret. A similar

effect has been shown in other situations of diagnostic uncertainty in medical decision making

(Simmons et al., 2003; Tait et al., 2009).

In the relational context, Snow et al. (2009) found self-reported pain in people with dementia

does not predict caregiver burden or relational strain four months later. In cognitively intact people,

including older couples, chronic pain has been shown to impact spousal relationships (Martire et al.,

2006). In long-term care settings, healthcare workers' distress and burden are strongly related to

residents' NPS, especially agitation, but are not related to residents' pain (Aasmul et al., 2016). It is

difficult to interpret these findings until more research is available. Nonetheless, these studies highlight

the importance and feasibility of assessing relational factors in pain in people with dementia.

Interestingly, they suggest differences between those with and without dementia in the impact of pain on

their caregivers' burden.

7. Integration among the dimensions: insights from imaging studies

The evidence reviewed above, despite its limitations, supports a biopsychosocial model in which pain and dementia have a reciprocal relationship. Support for the inter-relationships of the different dimensions of pain comes from studies of pain neural networks in people with dementia. Dementia, in particular AD, is associated with damage to multiple brain networks (Damoiseaux et al., 2012; Monroe et al., 2017), many of which overlap with the pain neuromatrix (Melzack, 2005, 2001). As a result, dementia-related brain pathology may impact on the processing of noxious stimulation, the creation of pain, and both behavioral and verbal responses to the experience (Scherder et al., 2003). Studies assessing brain activation and connectivity in response to painful stimulation in people with dementia compared to healthy controls have been used to examine this issue. Although it is difficult to integrate across existing studies because of methodological variation, taken together they suggest the patterns of activation and connectivity between various brain regions and networks is altered in people with AD [For a review of this topic, see Monroe et al. (2012)]. While the details are beyond the scope of the present paper, a broad summary would be that there are both increases (Cole et al., 2011, 2006) and decreases (Monroe et al., 2017) in functional connectivity between brain regions involved in pain sensitivity, modulation, and affect in people with AD compared to controls. In addition, while similarity in somatosensory evoked potentials between people with AD and healthy controls have been reported (Jensen-Dahm et al., 2015c; Limongi et al., 2013), there is also evidence for changes in the affective and cognitive responses to painful stimulation (Limongi et al., 2013). Interestingly, Monroe et al. (2017) found self-reported pain unpleasantness and connectivity are moderately correlated in healthy controls but not correlated in people with AD, raising intriguing possibilities regarding the impact of dementia on the relationships between brain activity and self-report of subjective experience. Taken together, the

preliminary evidence available supports our model by suggesting dementia has nonuniform effects across the different dimensions of pain and their interconnections (Monroe et al., 2012).

8. Conclusions and Future Directions

Although much more research is needed, a few conclusions can be drawn from the evidence we have reviewed. The most important are that about half of people with dementia, whether in community or institutional settings, report pain and that depression is a significant burden for many of these people. We have proposed that pain in older people with dementia is the result of an intricate network of interactions between three biopsychosocial phenomena and that dementia and pain have a reciprocal relationship. This relationship; however, is not uniform across the dimensions of pain. Rather, it appears the cognitive and affective dimensions are more directly impacted than the sensory, at least in the earlier stages of the illness. It is likely these relationships vary across dementia subtypes and as dementia progresses. A plethora of gaps in our knowledge and directions for future research has emerged. Future research that takes a biopsychosocial approach to the study of pain, aging, and dementia is needed. This research should include prospective, longitudinal studies with samples large enough to enable examination of key questions across dementia subtypes and stages. Another important direction will be the integration of the experimental and clinical research streams and a mapping of the generalizability of findings across different pain types and models. However, prior to this, in order for this field to advance, it is essential to determine a valid and reliable way to measure pain that is sensitive to the unique cognitive, linguistic, and behavioral characteristics of people with dementia, across the trajectory of dementia progression. It is vital that this measure not confound observer biases and symptoms of dementia with pain. As a preliminary step, further delineation of observer bias and more sophisticated understanding of symptom overlap and interrelatedness would contribute to the development and implementation of strategies to assess pain in people with limited verbal abilities. Further validation and

refinement of the many existing tools and identification of the most sensitive elements across tools for use given the subtype and stage of dementia also is needed (Gagliese, 2009). Once we can measure pain validly, then we can begin to elucidate the mechanisms of pain in dementia spanning peripheral and central neurobiological substrates and their interactions to considering lifelong and current biological, psychological, and social predisposing and buffering factors. This knowledge will make possible the development, testing and implementation of safe and effective pain management strategies to relieve unnecessary suffering in older people with dementia and pain.

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