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Review article

On the interplay between chronic pain and age with regard to neurocognitive integrity: Two interacting conditions?

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ABSTRACT

In this article, the interrelatedness of age and chronic pain is discussed and testable hypotheses about this interrelationship are postulated. Numerous studies have consistently shown mild cognitive problems, together with changes in brain gray and white matter integrity, in chronic pain patients. More recently, a handful of studies have indicated that age may play a crucial role in the reduced neurocognitive integrity in these chronic pain patients. However, studies systematically examining this interrelationship are lacking. We now give several propositions of this interaction between age and chronic pain by summarizing the evidence for the following testable hypotheses: 1) neurocognitive deficits in chronic pain are age-dependent, 2) chronic pain induces early aging, or 3) chronic pain can be considered as an age accelerator, resulting in a disproportional decline in neurocognitive integrity with increasing age. To advance this important field, it is highly recommended that future studies systematically document cognitive and neuroanatomical changes in chronic pain patients as a function of age.

Contents

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1. Introduction

Research has rather consistently demonstrated diminished cognitive functioning as well as reduced brain gray and white matter integrity in chronic pain patients. Interestingly, these cognitive and brain changes associated with chronic pain states strongly resemble those observed as a consequence of aging. Recently, a handful of studies have shown that age may play an important role in the presence and/or severity of the reduced neurocognitive integrity findings in chronic pain, which is suggestive of an interrelationship between age and pain. An important question is therefore whether the effects of chronic pain on brain structure and function can, and should, be examined in the context of aging.

In this article, the interrelatedness of age and chronic pain will be discussed. First, an overview is given of neurocognitive changes in aging and chronic pain separately to identify those domains most strongly affected by each condition. Next, similarities in neurocognitive changes in aging and chronic pain are discussed, and support is provided for the proposition that many of the studies conducted in chronic pain patients are confounded by age. Specifically studies are highlighted that focused on younger pain patients, since most studies that demonstrated neurocognitive problems linked to chronic pain included older pain patients, which complicates disentangling these two factors. Finally, the few available studies that reported potential effects of age in addition to chronic pain are reviewed. Based on these findings, three distinct hypotheses are proposed on the interrelationship between aging and chronic pain that will be discussed in detail below.

2. Neurocognitive changes in aging

Aging is associated with a decline in various cognitive functions (e.g., Park et al., 2002), such as executive function (including working memory), psychomotor speed, attention and episodic memory performance (Park et al., 1996, 2002; Salthouse et al., 2003). Several studies have shown that a decline in cognition is particularly present from the age of approximately 40–50 years (Borella et al., 2008; De Luca et al., 2003). This is substantiated by studies showing that aging-related declines in structural brain integrity become apparent around that age, including changes in white matter integrity (Fjell et al., 2013; Jernigan et al., 2001; Lebel et al., 2012; Raz et al., 2010), hippocampal gray matter volume (around the end of the fifth decade of life; Chowdhury et al., 2011; Fjell et al., 2013; Jernigan et al., 2001), the frontal lobes and anterior cingulate cortices (Jernigan et al., 2001; Raz et al., 1997). These alterations in gray and white matter integrity have subsequently been associated with the aging-related changes in cognitive function. For example, white matter changes and reduced hippocampal and prefrontal gray matter integrity have been associated with psychomotor speed (Papp et al., 2014), executive functioning (Oosterman et al., 2008; Papp et al., 2014), and episodic memory performance (Head et al., 2008).

Taken together, the effects of age become apparent from around middle age (i.e. the fifth decade of life) and profoundly affect frontal and medial temporal lobe gray and white matter integrity, which likely underlie the consistently reported mild declines in executive function, processing speed, episodic memory and attention in aging subjects.

3. Neurocognitive changes in chronic pain and similarities with aging

Many studies have shown that chronic pain patients present with mild cognitive decline, and neuroanatomical changes have been found in these patients as well. Diminished cognitive functions include executive processes, episodic memory, attention, and psychomotor speed (see Moriarty et al., 2011; Berryman et al., 2013, 2014, for reviews). These cognitive changes strongly resemble those observed in aging. Moreover, decreases in gray matter have been reported in several areas which are also particularly vulnerable to the effects of aging, including the (pre)frontal cortex, insula, and anterior cingulate cortex (ACC) (Cauda et al., 2014; Smallwood et al., 2013), whereas the hippocampal and parahippocampal regions may show increased gray matter density (Smallwood et al., 2013, but see Ezzati et al., 2014; McCrae et al., 2015; Zimmerman et al., 2009, for conflicting results). Only few studies examined the relationship between cognition and structural brain changes in chronic pain so far; one study reported that visual working memory was associated with gray matter changes in the dorsolateral prefrontal cortex in fibromyalgia patients (Luerding et al., 2008), an area vulnerable to the effects of aging as well. Finally, pain has also been associated with alterations in white matter integrity (Lin, 2014) and in other (not specifically aging-related) brain anatomical regions, including the thalamus and somatosensory cortices (e.g., Cauda et al., 2014; Lin, 2014; Smallwood et al., 2013).

Overall, it can be concluded that there is a strong overlap between those neurocognitive substrates affected as a result of aging and those typically compromised in chronic pain. This is not surprising, as an in-depth examination of the chronic pain literature available so far shows that the vast majority of studies focused on middle-aged or elderly patients when examining neurocognitive outcome measures. For example, of those studies examining cognitive performance, many reported an average age within the first half (e.g., Apkarian et al., 2004; Grisart and Van der Linden, 2001; Grisart et al., 2002, 2007; Harman and Ruyak, 2005; Sjøgren et al., 2005), or second half (e.g., Dick and Rashiq 2007; Dick et al., 2008; Grace et al., 1999; Grisart and Plaghki, 1999; Jamison et al., 2003; Park et al., 2001; Tassain et al., 2003; Veldhuijzen et al., 2006a,b; Verdejo-García et al., 2009) of the fifth decade of life, or even older (e.g., Dick et al., 2002; Karp et al., 2006; Lee et al., 2010; Luerding et al., 2008; Oosterman et al., 2011, 2012; Povedano et al., 2007; Rodríguez-Andreu et al., 2009; Sjøgren et al., 2000a,b; Weiner et al., 2006). This relatively high average age of pain patients targeted in different studies may be caused by the fact that age is a major risk factor for chronic pain and that for several painful conditions, the prevalence may reach a peak around middle-age (e.g., Andersson et al., 1993; Woolf and Pfleger, 2003). Nonetheless, this also implies that in these studies, a substantial number of the participants were of an age that fell within the fifth decade of life (or an even later decade), which is precisely the age range at which declines in cognitive function and brain morphology can be expected (as was described in Section 2). Even though most studies used age-matched control participants to demonstrate some unique effects of chronic pain on cognitive functioning, this currently does not entirely answer the question of whether the effects of chronic pain are to some extent dependent on, or intertwined with, those of aging. This interrelation between age and