On the moderating role of age in the relationship between pain and cognition

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Abstract

Background: A relationship between pain perception and cognitive function is evident. However, the directionality of this association is unclear and may be influenced by age. That is, inverse associations between pain and cognition have been reported in young and middle-aged chronic pain patients, whereas higher clinical pain ratings have been associated with better cognitive performance in older chronic pain patients. Therefore, this study examined the possible moderating role of age in the pain-cognition relationship.

Method: Twenty-two younger and 24 older chronic pain participants completed neuropsychological tests of psychomotor speed, memory and executive function. They also completed the McGill Pain Questionnaire to evaluate clinical pain.

Results: Interaction analyses revealed that age indeed moderates the relationship between clinical pain ratings and cognitive functions. In the younger age group, pain ratings were inversely related to memory and executive function. In the older age group, a positive relationship was found between pain ratings and executive function, whereas the inverse association of clinical pain with memory was no longer present.

Conclusions: This study was the first to confirm the hypothesis that age is an important moderator of the relationship between pain and cognition. An important finding is that in older adults, most inverse effects of pain on cognition are either no longer present or may even be reversed. The positive relationship between pain and executive function may indicate age-related reduced integrity of a shared underlying neural substrate.

1. Introduction

Many studies have been conducted in an attempt to better understand the relationship between chronic pain and cognition. These studies provided evidence for lower cognitive performance in chronic pain patients on tests of memory, attention, speed and executive functions (Moriarty et al., 2011). Moreover, many studies revealed an inverse association between pain intensity and cognitive performance (Weiner et al., 2006; Oosterman et al., 2011a). These findings support the hypothesis that the presence of pain competes with the available attentional resources, resulting in decreased cognitive performance as the level of pain increases (Eccleston, 1995; Grisart and Plaghki, 1999). As such, in young-to-middle–aged individuals, there appears to be a direct negative effect of pain on cognition.

What's already known about this topic?
- In middle-aged adults with chronic pain, higher clinical pain levels are associated with lower cognitive test performance.
- In older adults, a few studies have revealed a positive association between clinical pain ratings and cognitive performance.

What does this study add?
- This study is the first to confirm that age moderates the relationship between pain and cognition.
- At an older age, pain is overall either not or positively associated with cognition.

In sharp contrast is the positive association that has been reported between cognitive function and pain ratings in older chronic pain participants. Such results have been observed in elderly people with dementia (Scherder et al., 2008) and in non-demented elderly individuals living in residential care facilities (Oosterman et al., 2009). A reduction in pain complaints has furthermore been associated with the presence of impaired cognitive functioning in institutionalized and home-dwelling elderly (e.g. Cohen-Mansfield and Marx, 1993; Parmelee et al., 1993; Mäntyselkä et al., 2004; Leong and Nuo, 2007). The contrasting findings between younger and older participants suggest that age may play a crucial role in the relationship between the level of pain that is reported and cognition. One possibility for this altered relationship between pain and cognition is that aging affects structural and functional integrity of brain structures involved not only in pain processing, but also in cognition. The relationship may therefore merely reflect age-related alterations to shared underlying neural substrates, resulting in a concurrent decline in pain report and cognitive function. Indeed, aging is known to affect functioning of the prefrontal cortex (PFC) (Raz et al., 2007; Head et al., 2009) and hippocampus (Raz et al., 2010; Chowdhury et al., 2011), brain regions that are involved in both pain processing (Coghill et al., 2003; Zimmerman et al., 2009) and executive function and memory (Head et al., 2008; Oosterman et al., 2008; Cardenas et al., 2011). By reducing the integrity of these brain regions, it might be the case that at an older age the direct negative effect of pain on cognition is no longer evident.

Taken together, age potentially moderates the relationship between pain and cognition. However, this role of age has not been investigated in detail as of yet. This study therefore aimed to test this important question. A moderating role can be considered present if the predictive value of pain for cognition differs as a function of age. Since studies in dementia are limited by a decline in communicative skills and comprehension of the concept of pain, we chose to assess independently living, non-demented individuals with chronic pain.

2. Materials and methods

2.1 Participants

A total of 22 younger participants (aged 19–40) and 24 older participants (aged 50–80) with chronic pain participated in this study (see Table 1). Fifty years of age was used as a cut-off point for the older group since changes in structural integrity of both grey and white matter become evident at that age (Bartzokis et al., 2001; Walhovd et al., 2005; Chowdhury et al., 2011). Education was measured with an ordinal rating scale ranging from 1 (less than primary education) to 7 (academic degree) (Verhage, 1964). Participants with chronic pain were included in cooperation with the Pain Clinic at the University Medical Centre Utrecht, the Netherlands, outpatient physical therapy clinics, through advertisement (i.e. pain internet sites and oral advertisement), or consisted of participants of a previous (unrelated) study (Oosterman et al., 2011b). All participants reported persistent pain for over 1 year (mean duration = 12.2 years, median = 7.0 years, range 1.1–51 years).

Exclusion criteria were history of stroke, neurodegenerative disorders, current severe depression, and alcohol or substance abuse. Participants in both age groups suffered from a heterogeneous range of pain conditions (e.g. visceral pain, musculoskeletal pain,

Table 1 Characteristics of the two age groups.

	Younger group	Older group
Age (years)	28.8 (7.1)	65.0 (8.4)
Sex (M/F)	2/20	6/18
Education	5.5 (4–7)	5 (2–6)
Opioid use	4	6
Pain duration	9.8 (8.8)	10.6 (12.2)
Pain aetiology		
Visceral pain	5	2
Musceloskeletal pain	15	18
Neuropathic pain	1	2
Other	1	2

Means (standard deviations) are reported for age and pain duration, frequencies are reported for sex distribution, pain aetiology and opioid use, and the median score (range) is reported for education. A median education score of 5 represents vocational education.

neuropathic pain; see Table 1). Several participants used more than one type of analgesic medication: 17 used paracetamol, 16 used a NSAID, 10 were on opioids, and one participant used a tricyclic antidepressant. Data collection was performed by independent, trained, test assistants. This study was approved by the Medical Ethics Committee of the University Medical Centre Utrecht. All participants signed an informed consent form.

2.2 Clinical pain

The McGill Pain Questionnaire was used to measure clinical pain experience (Van der Kloot et al., 1995). Four subscales of this questionnaire were used in the present study. The current, minimum and maximum pain intensity levels were rated on a 10-cm visual analogue scale (VAS). These three VAS ratings were combined into a single average VAS score for the analyses. In addition, participants completed the Pain Rating Index (PRI), which is based on numerical values that are assigned to word descriptors representing pain sensations, taking into account the severity and quality of the sensation.

2.3 Cognitive tasks

All participants completed tests of psychomotor speed, executive function and episodic memory. Psychomotor speed was assessed with the Word and Colour cards of the Stroop test (Mead et al., 2002) and the Trail Making Test (TMT) part A (Bowie and Harvey, 2006). Executive function was measured using the TMT-B-ratio score (TMT-B divided by the TMT-A), the Stroop interference score (Stroop Colour/Word card divided by the Stroop Colour card) and the Letter Fluency test (Schmand et al., 2008). Finally, episodic memory was assessed with the Story Recall subtest (immediate and delayed recall) of the Rivermead Behavioural Memory test (Wilson et al., 1985).

2.4 Statistical analysis

Chi-squared tests were employed to test age group differences in sex, opioid use and pain aetiology. A t-test was employed to examine potential differences in pain duration between the age groups and Mann–Whitney U-tests to examine potential confounding effects of opioid use on cognitive performance.

The basic hypothesis of this study is that pain negatively affects cognition at a younger age, whereas the aging process may result in the loss of this negative effect of pain. To examine that age indeed moderates the effects of pain on cognition, the interactions

between age and the clinical pain scores were analysed. We performed hierarchical regression analyses with each neuropsychological test score as the dependent outcome variable. Main effects of age group (younger vs. older group) and pain rating (i.e. VAS or PRI) were entered as the first model; the interaction term was entered as the second model. This analysis was performed with each pain score (the VAS and the PRI) for each neuropsychological test score separately. For all analyses, a significance level of $p < 0.05$ was employed.

3. Results

No difference in sex [$\chi^2(1) = 2.02$, $p = 0.16$], opioid use [$\chi^2(1) = 0.31$, $p = 0.58$], pain aetiology [$\chi^2(1) = 2.14$, $p = 0.54$] or pain duration [$t(1) = -0.24$, $p = 0.81$] was present between the two age groups. Mann–Whitney U-tests did not reveal a significant difference between the participants using opioids ($n = 10$) and the participants not using opioids ($n = 36$) with regard to memory measured with immediate ($U = 173.0$, $p = 0.85$) and delayed ($U = 157.5$, $p = 0.55$) Story Recall performance, psychomotor speed as measured with the Stroop Colour Card ($U = 239.0$, $p = 0.12$) or the TMT-A ($U = 183.0$, $p = 0.94$), or executive function as measured with the TMT-B-ratio score ($U = 237.0$, $p = 0.13$), the Stroop interference score ($U = 163.0$, $p = 0.65$) or Letter Fluency score ($U = 131.0$, $p = 0.19$). A single significant difference was found for the Stroop Word card ($U = 270.5$, $p = 0.02$); reading performance was slower in patients on opioid medication (51.5 ± 11.1 s) compared with the non-opioid group (43.0 ± 6.3 s).

3.1 Age as a moderator

Logarithmic transformation was used to normalize the Stroop Colour card score, the Stroop interference score and the TMT-B ratio score. Results of the interaction analyses are presented in Table 2. Significant interactions were found between age and the average VAS score for immediate memory and for the TMT-B-ratio score, whereas a marginally significant effect was present for delayed memory. The interaction between age group and the PRI was marginally significant for immediate and delayed memory, as well as for the Stroop Colour card. To examine these interactions, the relationship between pain and cognition was plotted separately for the younger and older age groups. Inspection of the simple slopes (Table 3, one-sided) revealed that at a younger age, an increase in VAS pain ratings is associated with a decrease in immediate and

Table 2 The interaction between age and pain for the different neuropsychological test scores.

	Immediate memory	Delayed memory	Stroop word	Stroop colour	TMT-A	Letter fluency	Stroop interference	TMT-B-ratio
Step 1								
Age (β)	−1.08*	−0.93*	0.40	0.04	0.05	−0.46	0.63	1.88***
VAS (β)	−0.60***	−0.45*	0.20	0.22	0.04	−0.22	0.10	0.36*
Step 2								
Age × VAS (β)	1.10**	0.94*	−0.43	0.09	0.18	0.48	−0.56	−1.67***
Total R^2	0.15**	0.09*	0.02	0.07	0.05	0.02	0.04	0.33***
Step 1								
Age (β)	−0.51	−0.55*	−0.16	−0.38	0.47	0.08	−0.24	0.59*
PRI (β)	−0.32	−0.32	−0.24	−0.24	0.23	0.14	−0.32	−0.06
Step 2								
Age × PRI (β)	0.54*	0.57*	0.07	0.54*	−0.25	−0.04	0.32	−0.40
Total R^2	0.08*	0.08*	0.04	0.08*	0.07	0.01	0.06	0.20

The standardized beta coefficients represent the values of the final model. A higher score on the memory and fluency tests represent better performance; on all other tests it represents worse performance. PRI, Pain Rating Index; TMT, Trail making Test; VAS, visual analogue scale.
*$p < 0.10$.
**$p < 0.05$.
***$p < 0.01$.

delayed memory performance and, marginally, with a decreased in executive function performance (the TMT-B ratio score). In addition, a similar pattern of results was found for the relationship between the PRI and immediate and delayed memory. Overall, these slopes indicate that at a younger age, increasing levels of clinical pain are associated with lower executive function and memory performance.

For older adults, examination of the simple slopes revealed a positive relationship between the VAS pain rating and the TMT-B ratio score. These findings indicate that at an older age, a *decrease* in VAS pain ratings is associated with lower executive function performance. Memory was not associated with the clinical pain ratings. Finally, a marginally significant effect was observed for the Stroop Colour card, indicating that higher PRI ratings are associated with longer comple-

tion times on this test. Fig. 1 displays the interaction between age and the average VAS pain rating for immediate memory and Fig. 2 illustrates the interaction between age and VAS pain rating for the TMT-B ratio score.

4. Discussion

In the present study, we examined the moderating role of age in the relationship between pain and cognition in participants with chronic pain. Such a moderating role of age was indeed found, suggesting that the negative effects of pain on cognition differ as a function of age. In younger adults, higher clinical pain ratings were associated with a decrease in executive function and memory performance. At an older age, this inverse relationship between pain and cognition

Table 3 Simple regression slopes of the interaction between age and pain for cognition.

	Immediate memory t(42)	Delayed memory t(42)	Stroop colour card t(42)	TMT-B-ratio t(42)
Age × VAS				
Younger age	−2.70***	−1.95**	−	1.41*
Older age	0.04	0.34	−	−3.38***
Age × PRI				
Younger age	−1.48*	−1.50*	−1.09	−
Older age	1.16	1.28	1.49*	−

Simple regression slopes are displayed for the younger and older age groups. Slopes are only presented if the interaction was significant. PRI, Pain Rating Index; TMT, Trail Making Test; VAS, visual analogue scale.
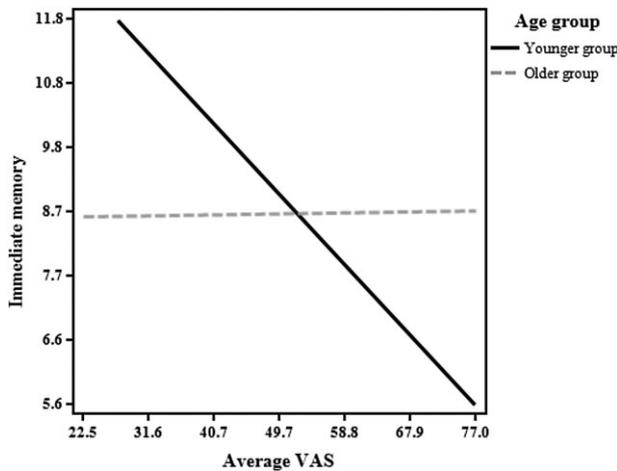*$p < 0.10$.
**$p < 0.05$.
***$p < 0.01$.

Figure 1 The moderating role of age in the relationship between visual analogue scale pain ratings and memory performance.

was largely absent. In addition, *lower* clinical pain ratings were associated with a decline in executive function performance. These findings add to the existing literature in that we demonstrate that age is an important determinant of the presence and directionality of the relationship between pain and cognition.

One important question is how the moderating role of age can be integrated in the causality that is often assumed in the relationship between pain and cognition. At a younger age, it is generally accepted that chronic pain has a negative impact on cognitive function. Pain is presumed to act as a distractor, capturing attention and leaving reduced resources available for other (cognitive) processes. At an older age, however, it is unlikely that the same mechanism is in operation,
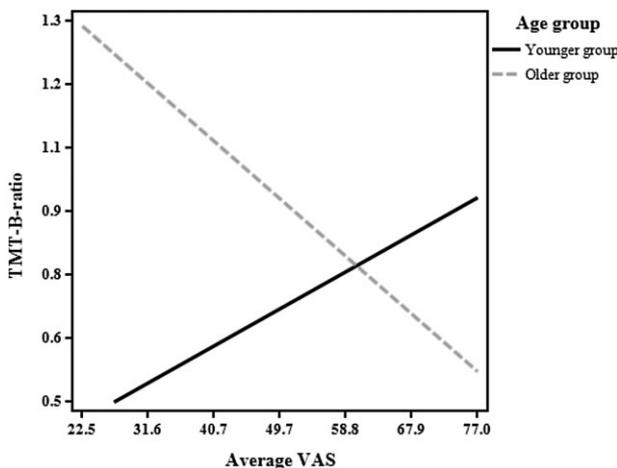

Figure 2 The moderating role of age in the relationship between visual analogue scale pain ratings and executive function.

since we demonstrated that, overall, pain was either not associated with cognitive test performance, or that the direction of relationship was reversed (i.e. positive). The latter was significant for executive task performance only. Thus, the distracting nature of pain did not result in lower cognitive task performance with increasing pain levels at an older age. The inverse relationship between pain and cognitive function, as observed at a younger age, might be obscured at an older age simply because with advanced age, there are other factors (apart from pain) that are more important in explaining cognitive decline (e.g. changes in brain vascularization). As many of these factors were unmeasured in the current study, we cannot compare the relative importance of pain versus these other issues. It is well-documented that cognitive functions decline with advancing age (Salthouse, 2009, 2011), regardless of the presence of pain. This may potentially interfere with the simple relationship between pain and cognition, whereas in young, healthy adults there are no such concerns.

An alternative explanation is that the altered pain–cognition relationship represents age-related reduced integrity of shared neural substrates, such as the PFC or the hippocampus. These brain regions are very important for executive function and memory, respectively, and both were types of cognition for which significant interactions between age and clinical pain ratings were present. However, it remains unclear why neurodegeneration of a shared neural substrate would result in a positive relationship between pain and cognition and not simply the loss of the pain–cognition relationship, nor why the positive relationship was only present for executive function. Previous studies also reported such positive relationships of clinical pain ratings with executive function, but not memory or psychomotor speed, in both non-demented institutionalized elderly (Oosterman et al., 2009) and patients with dementia due to Alzheimer's disease (Scherder et al., 2008). Whether this positive relationship indicates that executive and/or PFC function is uniquely involved in clinical pain reports (e.g. through pain awareness; Oosterman et al., 2009) or whether it merely indicates that these functions are most sensitive to the effects of aging, remains to be elucidated.

It is important to realize that the positive relationship between pain and cognition at an older age was present for a single executive function task only. This might indicate that it is crucial to distinguish between different cognitive tests (Oosterman et al., 2010), but it may also simply reflect insufficient power because of a small sample size. Also, executive function might be one of the functions most sensitive to the effects of

pain (Moriarty et al., 2011, but see also Oosterman et al., 2012). Further studies are therefore needed that examine the moderating role of age in larger study samples. In addition, a limitation of the present study is the heterogeneous aetiology of chronic pain in our participants as well as the heterogeneity in medication use. We expect that these factors do not crucially affect our study results since no group differences were present with regard to aetiology of pain, and because opioid use was not associated with any of the neuropsychological tests for which an interaction between age and pain was present. It is, however, crucial to replicate these findings in a more homogeneous study sample.

In this study, we provide clear evidence for a moderating role of age in the relationship between pain and cognition. More particularly, whereas at a younger age inverse associations exist between cognition and pain severity, at an older age this relationship is mostly absent or potentially reversed with less pain being reported in the context of lower executive ability. One important notion is, however, that this does not necessarily imply a reduction in the amount of pain that is *experienced*. It may actually be the other way around: in case cognitive (or more specifically, executive) function is diminished, one should always consider the possibility that more pain is experienced than is reported. This explanation could also account for the discrepancy that has been reported in (Alzheimer) dementia patients, in whom lower clinical pain ratings (Scherder et al., 1999) contradict the fact that these patients seem to experience a similar level of pain, or perhaps even more, as indicated by pain observation scales and experimental painful stimulation (Kunz et al., 2007, 2009; Scherder et al., 2009).

To summarize, the inverse relationship between pain and cognition seen in young adults is either absent or reversed at an older age. The relationship between pain and cognition is complex and further studies of how this relationship changes as a function of age are needed.

Author contributions

JMO designed the study and WLJAP was involved in the data collection. JMO, SG and DSV wrote the paper and were responsible for the statistical design of the study and for carrying out the statistical analysis. All authors discussed the results and commented on the manuscript.

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