Pain and cognitive functioning in community-dwelling older adults

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Pain and cognitive functioning in community-dwelling older adults

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geboren te Geleen

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	prof.dr. J. Verghese
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Chapter 1

General introduction

General introduction

The problems faced

In the Netherlands, as well as in the United States, a demographic shift towards an ageing population is taking place. The generation of people born in the years after the Second World War, which has been coined 'the baby boom generation', is currently forming a substantial part of the population in both countries. This demographic change causes a significant increase in health care costs [1,2] given their longer life expectancy and aging-associated diseases. With an aging population, government policies have focused on maintaining the independence of elderly people. In the Netherlands, the responsibility of care for the elderly patient is mainly provided by primary care providers and these patients are now living at home longer. In order to promote the well-being of older individuals (often referring to people aged 65 years and older) and contain the costs of health care, prolonged independence is desirable. Independent living and functioning might be hampered by several factors, such as chronic pain, decrease of mobility and of cognitive functioning, factors which might negatively interact with each other.

It has been suggested that chronic pain should receive more attention as a global health priority, and the treatment of pain is regarded as a human right with the duty of any health care system to provide it [3]. Adults frequently report chronic pain; in Europe, 19% of all adults experience moderate or severe chronic pain, with a similar prevalence of 18% in the Netherlands [4]. This prevalence increases with advancing age: more than half of the community-dwelling older adults and up to 70% of older adults in residential homes experience chronic pain [5-7]. In several studies an association between chronic pain and impaired cognitive functioning has been found [8,9]. However, most of the studies published on this topic were performed in small samples, were restricted to limited domains of cognitive functioning or applied a cross-sectional design [10-15]. Less is known about the temporality of this relationship and whether pain is associated with various domains of cognition and pre-dementia syndromes, such as the Motoric Cognitive Risk Syndrome (MCR). Also possible mechanisms, explaining how chronic pain might be associated with cognition, have received little attention until now.

The aim of our studies is to clarify the association between chronic pain and several domains of cognitive functioning in older adults. Establishing a cross-sectional and longitudinal association of chronic pain severity with specific cognitive domains and exploring a possible mechanism may shed light on a potentially modifiable risk factor for cognitive impairment in aging.

In this chapter, we provide background information on topics relevant for our research including definitions of pain and cognitive functioning and the operationalization of these definitions in our studies, finishing with the aims and outline of the thesis.

Chronic pain

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described as such damage" [16]. Pain is often caused by an injury or disease. However, when pain becomes chronic it is more than an accompanying symptom, it can be considered as a separate condition. While acute pain functions as an alert system to indicate possible injury, in chronic pain signals keep firing in the nervous system without any acute threat [17]. Pain is usually regarded as chronic when it lasts or recurs for more than 3 to 6 months [18]. However, the IASP defines chronic pain as 'pain that has persisted beyond the normal tissue healing time' [16].

Recently, the International Classification of Diseases, 11th Revision (ICD-11), has developed for the first time a code for chronic pain, persisting or recurring for more than 3 months, including chronic primary pain and chronic secondary pain [19,20].

In our studies, we use three different datasets described in the paragraph titled 'Datasets' later on in the Introduction. Each dataset includes different pain questionnaires. In the Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly (MOBILIZE) Boston Study, pain severity (pain "you have today that you have experienced for more than just a week or two") and pain interference during the past week with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life were assessed. In the Central Control of Mobility in Aging (CCMA) study, bodily pain severity in the past four weeks was assessed. In the Health and Retirement Study (HRS), no duration was included in the pain questionnaire; participants were asked if they are often troubled with pain. None of the questionnaires in these studies includes a pain duration of more than 3 months or assumes a duration longer than the expected healing time. Therefore, we are not sure that participants in our datasets actually had chronic pain according to the definitions mentioned above, especially those participating in the HRS. However, including participants with acute pain might only underestimate the possible long-term effects of chronic pain. We will discuss this further as a limitation of our studies in the Discussion section.

Pain in older adults

In a telephone-survey taken in 15 European countries and Israel, 19% of 46.394 adults reported chronic pain (chronicity was defined as pain lasting more than 6 months, which was present during the last month and several times during the last week). The most

commonly reported causes of chronic pain were osteoarthritis and rheumatoid arthritis (42%), followed by pain from herniated or deteriorated discs, fractures or deterioration of the spine (20%), pain caused by physical trauma or surgery (15%). Less than 10% of the patients reported pain due to migraine headaches, while in 4% nerve damage or whiplash and in 1% cancer appeared to be the cause. 12% of the respondents did not know the cause of their pain [4]. Central sensitization, a process in the central nervous system referring to a persistent state of high reactivity, which subsequently lowers the threshold for experiencing pain, is an important mechanism in the development to chronic pain [21,22].

Chronic pain in older adults can have detrimental effects on performing daily activities, and has been associated with falls [23,24], mobility disability [25], functional impairment and poor self-rated health [10,26-28]. Chronic pain may also affect cognition in older adults [8]. Previous studies on pain and cognition often focused on a single pain location or single domain such as chronic low back pain and pain intensity [13,15]. In our study we aim to provide a more comprehensive overview of the association between pain and cognition, since we are studying various domains of pain and cognition.

Cognitive functioning

Cognitive functioning has been described as the brain's acquisition, processing, storage and retrieval of information [29]. However, cognition may also be considered as an umbrella term describing integrative neuropsychological processes [9]. Impaired functioning in any of these domains is likely to impact nearly every aspect of independent living, including daily self-care, health maintenance and social activity. Persons with impaired cognitive functioning are at a greater risk for physical disability, hospitalization and death [30-32].

In our research, we focus on several domains of cognitive functioning, including attention, executive functioning, memory and general cognitive performance, which could be seen as an umbrella term covering various domains of cognitive functioning. These included cognitive domains are likely to be particularly relevant to daily functioning. Different terms of diminished cognitive functioning are used, including cognitive impairment and cognitive decline, according to definitions used in particular studies.

Pain and cognitive functioning

Since previous studies on pain and cognition often focused on a single domain of cognitive functioning [10-15], we want to know whether pain interference and severity interferes with several domains of cognitive functioning, including attention, executive functioning, memory, and general cognitive performance. We want to investigate the association between chronic pain and these domains of cognitive functioning in older adults.

It has been suggested that pain demands attention, which can result in poorer performance on attention-demanding cognitive tests. The Eccleston cognitive-affective theory describes that pain demands attention and takes precedence over other attention-demanding cognitive tasks [33]. The research question rises whether chronic pain is associated with poorer cognitive functioning in the attentional domain. The Test of Everyday Attention (TEA) [34,35] is designed to measure attentional abilities during tasks resembling everyday activities in persons aged 18-80 years old and measures four domains of attention: attentional shifting, selective, sustained, and divided attention. However, it is still unknown if the TEA is also a valuable measure of attentional resources in very old adults (>80 years). We want to analyze if the TEA is a valuable tool to measure attention in our study population. We also want to examine the cross-sectional association between pain and several domains of attention in older adults.

After exploring the cross-sectional associations between pain and cognitive functioning, we focus on the possible longitudinal association. Longitudinal studies in this field are lacking and therefore no conclusions can be drawn about the temporality of the association between pain and cognition. Only one study showed that older adults with persistent pain are at higher risk for accelerated memory decline and have an increased risk of dementia [36]. Therefore, the question rises whether older adults with more severe pain have a higher risk of developing cognitive decline (on the attention, executive functioning, and memory domain), compared to their counterparts with mild pain or without pain. Thus we will examine the longitudinal association between pain and cognitive function in older adults.

Next the question comes up which mechanism could be responsible for the association between pain and cognition. Moriarty and colleagues have described several mechanisms how pain can effect cognitive functioning, for instance through neurochemical mediators, released during pain [9]. Among these mediators are pro-inflammatory cytokines, such as C-reactive protein (CRP). Clarifying the possible mediating role of CRP in the relationship between pain and cognition might be an important step towards the development of strategies to reduce the pain related cognitive effects by lowering CRP-levels, if CRP turns out to be a mediator. We aim to clarify the possible mediating role of CRP on the pain-cognition relationship.

Finally, we focus on pain and the Motoric Cognitive Risk Syndrome (MCR), a pre-dementia syndrome. Previous studies have reported associations between pain and slow gait and pain and cognitive impairment. While both of these symptoms are key components of the MCR definition, it is yet unknown whether pain also predicts MCR. Our final aim is to enhance our understanding of the association between pain and the Motoric Cognitive Risk Syndrome.

Datasets

We have data from three different independent cohorts at our disposal and we use these data to answer our research questions;

1. *MOBILIZE Boston study*

   The Maintenance of Balance, Independent Living, Intellect, and Zest in de Elderly (MOBILIZE) Boston Study is a population-based study of 765 participants aged 70 and older. Pain was measured according to pain severity and interference using the Brief Pain Inventory subscales. The neuropsychological battery included measures of attentional capacity (Trail Making Test A, WORLD test), executive function (Trail Making Test B and Delta, Clock-in-a-box, Letter Fluency), and memory (Hopkins Verbal Learning Test). In the sixth-year follow-up assessment of the population-based MOBILIZE Boston Study, referred to as MOBILIZE II, four subscales of the Test of Everyday Attention (TEA) were added in order to measure domains of attention; attentional switching, and selective, sustained, and divided attention.

2. *Central Control of Mobility in Aging study*

   We also used data from the Central Control of Mobility in Aging study (CCMA), in which 590 community-residing individuals without dementia, age 65 and older enrolled between June 2011 and September 2017. Pain severity is measured using the 20-point Medical Outcomes Study pain severity scale. The CCMA contains a large battery of cognitive tests, including the RBANS (The Repeatable Battery for the Assessment of Neuropsychological Status) measuring attention and memory and the Trail Making Test Delta, measuring executive functioning. Also, MCR syndrome diagnosis is included.

3. *The Health and Retirement Study*

   The ongoing Health and Retirement Study (HRS) is a nationally representative longitudinal survey of more than 37 000 individuals older than 50 years old in the US. The sample was build up over time and the initial cohort enrolled adults aged between 51 and 61 (born between 1931 and 1941) in 1992. The HRS later merged with additional cohorts to become a national representative cohort of U.S. community-dwelling adults aged 51 years and older in 1998 [37]. Core interviews were conducted every two years with a mixed design of telephone and face-to-face interviews. In-home-visits were implemented in 2004 and this was expanded to include the whole sample in 2006 and 2008. Pain severity was included and based on four categories (no pain, mild, moderate, or severe). The Telephone Interview for Cognitive Status (TICS) (adapted to be administered in-person and by telephone), was used to measure cognition [38,39]. MCR diagnosis is also included. C-reactive protein (CRP) level was used as the measure of inflammation.

Outline of this thesis

In *chapter 2*, we describe the association between pain (interference and severity) and general cognitive performance and several domains of cognition, including attention, executive functioning and memory. Then we focus on the question whether the TEA is a valuable tool to measure attention in very old adults (>80 years) in *chapter 3,* and subsequently we report the association between pain and the before mentioned domains of attention in *chapter 4*. In *chapter 5*, we describe whether older adults with more severe pain have a higher risk of developing cognitive impairment (on the attention, executive functioning, and memory domain), compared to their counterparts with mild or without pain. In *chapter 6*, we report the possible mediating effect of CRP on the association between pain and cognition. In *chapter 7*, we focus on the association between pain and prevalent and incident MCR in two independent datasets. Finally, in *chapter 8* we discuss the main findings, methodological aspects, clinical implications of our findings and we provide suggestions for future research.

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CHAPTER 2

PAIN AND COGNITIVE FUNCTIONING AMONG OLDER ADULTS LIVING IN THE COMMUNITY

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Abstract

Background: Pain related to many age-related chronic conditions is a burdensome problem in older adults and may also interfere with cognitive functioning. The purpose of this study was to examine the cross-sectional relationship between measures of pain severity and pain interference and cognitive performance in community-living older adults.

Methods: We studied 765 participants in the Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly (MOBILIZE) Boston Study, a population-based study of persons aged 70 and older. Global pain severity and interference was measured using the Brief Pain Inventory subscales. The neuropsychological battery included measures of attentional capacity (Trail Making Test A, WORLD test), executive function (Trail Making Test B and Delta, Clock-in-a-Box, Letter Fluency), memory (Hopkins Verbal Learning Test) and a global composite measure of cognitive function. Multivariable linear regression models were used to analyze the relationship between pain and cognitive functioning.

Results: Elderly with more severe pain or more pain interference had poorer performance on memory tests and executive functioning compared to elders with none or less pain. Pain interference was also associated with impaired attentional capacity. Additional adjustment for chronic conditions, behaviors and psychiatric medication resulted in attenuation of many of the observed associations. However, the association between pain interference and memory and general cognitive function persisted.

Conclusions: Our findings point to the need for further research to understand how chronic pain may contribute to decline in cognitive function, and to determine strategies that may help in preventing or managing these potential consequences of pain on cognitive function in older adults.

Introduction

In 2005, it was estimated that more than 21,000,000 persons aged 65 or older in the United States were living with arthritis or chronic joint symptoms and this number is expected to double by 2030[1]. Pain is a frequently reported problem, considering that more than half of the older population experiences chronic pain[2].

Chronic pain interferes with daily functioning in older adults and often results in severe physical disability and mobility disability[3-5]. It is reported as one of the primary causes of disability and physician office visits in the elderly[6,7]. Non-cancer pain and cognitive impairment have both been associated with functional disability, with even a greater functional burden when both conditions are present[8]. With advancing age, maintenance of mobility and performance of daily activities largely depends on intact cognitive functioning[9-12]. Decline in cognitive functioning can make older adults who are already vulnerable to falls and fall-related injuries even more susceptible to these problems[13,14].

In clinical samples of older adults, chronic low back pain has been associated with poorer cognitive function[15]. The few studies published on this topic were mainly performed in small samples and were restricted to limited assessments of cognitive functioning. In those studies, chronic pain was associated with poorer cognitive functioning in the domains of memory, mental flexibility, emotional decision-making, and attention[16-20]. Other studies also suggested a relationship between chronic pain and attention, psychomotor speed and processing speed, memory, and mental flexibility in adults across age groups[15,19,21].

Pain in older adults may lead to poorer cognitive function because the presence of pain may require attention and may compete for limited attentional resources[22]. The aforementioned studies suggest that other domains of cognitive functioning are also affected by the presence of pain. It is possible that pain may co-occur with or exacerbate cognitive decline related to brain changes associated with aging.

Given the possible detrimental effects of pain on cognition, coupled with the growing recognition of the role of age-associated changes in brain function on balance and mobility decline in old age[23,24], it is important to better understand the pain-cognition relationship in the older population. The major premise of this study is that pain interferes with cognitive functioning, because pain is distracting and challenges attentional resources. We hypothesize that, compared to older adults with no pain or mild pain, those who have more severe pain or pain interference with activities will have poorer cognitive functioning in areas of attention, memory and executive functioning.

Methods

The Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly (MOBILIZE) Boston Study is a population-based cohort study of mobility and falls in persons aged 70 and older living in the community in and around Boston. At baseline, 765 participants completed the health interview and clinic assessment. Eligibility criteria for study participation included aged 70 years and older, understands and communicates in English, and able to walk 20 feet independently. The sample also included 16 participants aged 65-69 years old and otherwise eligible who were allowed to join the study because they were living with a study participant. People with moderate or severe cognitive impairment, determined by a Mini Mental State Examination (MMSE) score less than 18, were excluded[25,26]. Before the baseline interview, participants provided informed consent. All methods and procedures were approved by the Institutional Review Boards of the Hebrew Senior Life and collaborating institutions. Detailed descriptions of the study design and methods are published elsewhere [27,28].

Measurements

This cross-sectional study used data from the baseline home interview, that included the extensive pain assessment and the neuropsychological battery conducted by trained research assistants. Training was performed by an experienced neuropsychologist, and using a certification procedure, research assistants were required to demonstrate skills in administration of the neuropsychological tests with older pilot study volunteers before proceeding with baseline assessments. Global pain was measured using the Brief Pain Inventory (BPI) pain severity and pain interference subscales[29,30].

For the BPI, participants were asked to rate their pain, described as pain "you have today that you have experienced for more than just a week or two". Pain severity was rated according to four conditions: at its worst and least in the past week, average pain, and pain now on a scale from 0 to 10, where 0 reflects 'no pain' and 10 reflects 'severe or excruciating pain, as bad as you can imagine'. The subscale score was the average of the 4 ratings, with scores ranging from 0 to 10. Although the tool was initially developed for measurement of pain in patients with cancer[30], the BPI pain severity subscale also has been validated in people with chronic non-malignant pain[29,31].

For the BPI pain interference subscale, participants rated the degree to which pain interfered during the past week with seven circumstances: general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life, referring to a 0 to 10 numeric rating scale, with 0 indicating no pain interference and 10 indicating complete interference[29]. The interference subscale score was the average of the 7 item ratings, with subscale scores ranging from 0 to 10.

Neuropsychological measures

The neuropsychological battery addressed three cognitive domains: attentional capacity, executive functioning, and memory.

Attentional capacity

The attentional domain includes the WORLD test, where participants were asked to spell the word 'WORLD' backwards. Scores range from 0 to 5 where higher scores reflect better performance[26].

The Trail Making test (TMT) part A includes number targets that must be connected sequentially (e.g. 1-2-3-4), providing information about visual attention and psychomotor speed[32,33]. Performance of TMT Parts A and B was based on the time in seconds required to complete each task up to a maximum of 300 seconds[32,33]. Shorter time reflects better performance.

Executive functioning

TMT Part B, TMT Delta, Clock-in-the-Box Test and the Letter Fluency Test (F, A, S words) provide estimates of executive functioning. TMT Part B contains numbers and letters that are to be connected in alternating succession (e.g. 1-A-2-B-3-C). Similarly to TMT Part A, a shorter time reflects better performance.

The TMT Delta was calculated by subtracting the time to perform Part A from the time to perform Part B. The difference score was used to control for the effect of information processing speed and motor function and is used in other studies as an indicator for executive functioning[34-36]. Besides executive functioning, the TMT has also been shown to measure visual search, scanning, processing speed, and mental flexibility[32]. The TMT has been shown to be sensitive to the presence of frontal-executive cognitive impairment and cerebrovascular risk[37].

The Clock-in-the-Box Test requires participants to read and follow written instructions where they are asked to draw a clock within a box and set the clock to the correct time. The test requires working memory for applying the written instructions and organization and planning for drawing[38,39].

In the Letter Fluency test, participants are asked to name as many words as possible beginning with the letters F, A, and S for 60 seconds each. A higher number of items generated indicates better cognitive performance, in particular, executive function[33].

Memory

The memory domain includes the subtests of the Hopkins Verbal Learning Test (HVLT). The HLVT is a 12-item word list learning test divided into Immediate recall and Delayed recall [40]. The Immediate recall score is calculated by the sum of correct responses directly after the words are read out loud. The Delayed recall is calculated by the sum of items correctly recalled after a 20-minute delay. Both executive functioning and working and verbal memory processes are required for the HLVT[41].

General Cognitive Function

We constructed a summary factor representing general cognitive performance from a factor analysis of the neuropsychological test battery used in the MOBILIZE Boston Study. The battery consisted of 5 tests, representing 7 variables. We used HVLT total and delayed recall, Trail Making Test parts A and B, phonemic (CFL words) and semantic fluency (for animals) [42], and clock-drawing. We scaled the factor to a nationally representative sample using the four tests in common (Trails A, B, phonemic and semantic fluency) between the MOBILIZE Boston Study and the Aging, Demographics, and Memory Study (ADAMS), a sub-study of the Health and Retirement Study (HRS)[43-45]. The summary factor was scaled to have a mean of 50 and SD of 10 in a nationally representative sample of older adults[46].

Participant characteristics and health measures

Sociodemographic characteristics assessed in the home interview included age, gender, race, and years of education. Analgesic medication and psychiatric medication use were assessed as part of the in-home medication review[27]. Major chronic conditions, including heart disease and the presence of diabetes and depression were assessed using interview and using laboratory information. Physical activity was measured using a validated instrument, the Physical Activity Scale for the Elderly (PASE) and the use of alcohol was measured based on self-reported number of drinks per day or week. These factors were all considered potential confounders of the relationship between pain and cognitive functioning. Among the elderly, those with lower education have been shown to be more at risk for cognitive decline[47]. Level of education was represented by two categories; high school or less (≤12 years of education), college attendance or higher (>12 years of education).

Statistical analysis

Participant characteristics were examined according to pain severity and interference scores. The mean pain scores were calculated and the differences according to baseline characteristics were tested using z-scores. Next, we created three similar models for pain severity and interference. The first unadjusted model was obtained through linear regression of the relationship between pain severity and pain interference and the

dependent variables, each of the scales in the neuropsychological battery and the global composite measure of cognitive function. Multiple linear regression models were used to investigate the relationship between pain measures and tests of cognitive functioning within each of the cognitive domains, adjusting for age, sex, race and education (Model 2). BPI pain severity and pain interference subscale scores were entered as ordinal variables. Subsequently, the third model included further adjustment, adding major chronic conditions including depression, physical activity, alcohol use, and use of psychiatric medications to the second model.

Also, the associations between the different pain measures and cognitive functioning were tested with additional adjustment for attention to Model 2, to control for the possible impact of attentional demands on the association between pain and cognition. We used the TMT Part A, described above, as a measure of attention.

There were no major outliers detected in the models. Because some data were skewed, we also used logarithmic transformations to normalize the data. The results for the transformed and non-transformed data did not differ from each other. Therefore we report only the analyses using non-transformed data. All analyses were performed with SPSS 21.0.

Results

Characteristics of the study sample

The overall sample of 765 participants had an average age of 78.1 years (SD=5.4) with 489 women (63.9%) and 276 (36.1%) men, reflective of the population of community-living elders in the Boston area, according to the 2000 US Census[27]. The average number of years of education was 14.2 years (SD=3.1) and the total sample was 77.6% white and 16.1% African-American.

One in four participants had BPI pain severity subscale scores of 4 or higher, indicative of at least moderate pain intensity overall. Only 21.4% of the sample had a zero score on the BPI severity subscale. For pain interference with daily routines, 16.5% of the cohort reported at least moderate pain interference (score ≥ 4 on the BPI interference subscale) and 38% reported zero interference from pain. Average pain severity and interference scores are displayed according to demographic characteristics in Table 1. Older adults with more severe pain or more pain interference were more likely to be women, African-American, and had fewer years of education.

Table 1. Demographic characteristics according to pain severity and pain interference among 765 adults aged 70 years and older, MOBILIZE Boston Study

		Brief Pain Inventory			
		Pain Severity	**p value***	**Pain Interference**	**p value***
Characteristic	**Total sample**	**Mean (SD)**		**Mean (SD)**	
Gender					
Women	63.9%	2.67 (2.19)	≤.001	1.87 (2.26)	.001
Men	36.1%	1.88 (1.95)		1.33 (1.95)	
Age (in years)					
Age 65-74	30.6%	2.35 (2.08)	.323	1.53 (2.02)	.327
Age 75-79	31.9%	2.55 (2.18)		1.65 (2.21)	
Age > 79	37.5%	2.27 (2.15)		1.82 (2.24)	
Race					
White	77.6%	2.20 (2.00)	≤.001	1.54 (2.07)	.006
Black	16.1%	3.20 (2.51)		2.20 (2.44)	
Other	6.3%	2.57 (2.31)		1.98 (2.49)	
Years of education					
≤ 12	34.4%	3.03 (2.35)	≤.001	2.23 (2.56)	≤.001
> 12	65.6%	2.04 (1.93)		1.38 (1.87)	

* p Values, using z-scores to compare means.

Initially, without adjusting for demographic or health characteristics, pain severity and pain interference scores were significantly associated with each of the neuropsychological tests. After adjusting for age, gender, race and education, significant associations were observed between pain severity scores and all the cognitive tests within the executive function and memory domains, except for Letter Fluency (Table 2 and 3). Pain interference scores showed significant associations with all cognitive tests, except for the WORLD test and Letter Fluency. Additional adjustment for chronic conditions and psychiatric medication resulted in attenuation of the effects, where only the relationship between pain interference and memory and general cognitive performance remained statistically significant. We performed additional adjustment for use of analgesics including opioids but it did not alter the results, thus we did not include analgesics in our final multivariable models.

Table 2. Association between pain severity and cognitive performance in adults aged 70 and older, MOBILIZE Boston Study

Cognitive test		Model 1		Model 2		Model 3	
		B (SE)*	p value	B (SE)*	p value	B (SE)*	p value
Attention	WORLD	-0.32 (0.15)	.042	<-0.01 (0.02)	.917	0.01 (0.02)	.458
	Trail A	2.50 (0.60)	≤.001	1.10 (0.57)	.055	0.21 (0.61)	.734
Exec. Function	Trail B	6.91 (1.39)	≤.001	2.85 (1.23)	.021	1.37 (1.29)	.289
	Trail Delta	5.31 (1.13)	≤.001	2.31 (1.05)	.028	1.51 (1.10)	.171
	Clock-in-a-box	-0.10 (0.03)	≤.001	-0.05 (0.03)	.031	-0.04 (0.03)	.161
	Letter Fluency	-1.11 (0.24)	≤.001	-0.39 (0.23)	.086	-0.38 (0.24)	.112
Memory	HVLT Im. Recall	-0.34 (0.09)	≤.001	-0.20 (0.09)	.024	-0.14 (0.09)	.139
	HVLT Del. Recall	-0.22 (0.06)	≤.001	-0.13 (0.06)	.020	-0.09 (0.06)	.114
	GCP	-0.71 (0.13)	≤.001	-0.32 (0.11)	.003	-0.20 (0.11)	.072

Notes: Model 1: Unadjusted linear regression model; Model 2: Adjusted for age, sex, race, and years of education; Model 3: Adjusted for age, sex, race, years of education, psychiatric medications, physical activity score (PASE), heart disease, diabetes, alcohol, and depression.
Del=Delayed; Exec=executive; GCP=general cognitive performance; HVLT=Hopkins Verbal Learning Test; Im=Immediate.
* Unstandardized regression coefficient and standard error (SE) from general linear regression models.

Table 3. Association between pain interference and cognitive performance in adults aged 70 and older, MOBILIZE Boston Study

Cognitive test		Model 1		Model 2		Model 3	
		B (SE)*	p value	B (SE)*	p value	B (SE)*	p value
Attention	WORLD	-0.05 (0.02)	.002	-0.03 (0.02)	.098	-0.01 (0.02)	.588
	Trail A	2.82 (0.59)	≤.001	1.64 (0.54)	.003	0.65 (0.62)	.301
Exec. Function	Trail B	6.50 (1.37)	≤.001	3.15 (1.18)	.008	1.53 (1.33)	.248
	Trail Delta	4.48 (1.12)	≤.001	2.01 (1.01)	.047	1.10 (1.13)	.333
	Clock-in-a-box	-0.12 (0.03)	≤.001	-0.07 (0.02)	.004	-0.05 (0.03)	.057
	Letter Fluency	-0.92 (0.24)	≤.001	-0.31 (0.22)	.150	-0.36 (0.24)	.146
Memory	HVLT Im. Recall	-0.47 (0.09)	≤.001	-0.32 (0.08)	≤.001	-0.28 (0.09)	.003
	HVLT Del. Recall	-0.31 (0.06)	≤.001	-0.23 (0.05)	≤.001	-0.21 (0.06)	.001
	GCP	-0.77 (0.12)	≤.001	-0.41 (0.11)	≤.001	-0.32 (0.11)	.006

Notes: Model 1: Unadjusted linear regression model; Model 2: Adjusted for age, sex, race, and years of education; Model 3: Adjusted for age, sex, race, years of education, psychiatric medications, physical activity score (PASE), heart disease, diabetes, alcohol, and depression.
Del=Delayed; Exec=executive; GCP=general cognitive performance; HVLT=Hopkins Verbal Learning Test; Im=Immediate.
* Unstandardized regression coefficient and standard error (SE) from general linear regression models.

To assess whether the attentional domain may be influencing the observed relationships, we performed additional adjustment for attention by adding TMT A to Model 2. We found that the associations between pain severity and the Clock-in-the-Box Test and HVLT Immediate and Delayed Recall were no longer statistically significant (unstandardized regression coefficient [p value]: -0.04 [.12]; -0.13 [.12]; -0.10 [.08], respectively). Also, the associations between pain interference and TMT Part B and Delta were no longer statistically significant after adjusting for attention (B [p-value]: 1.69 [.09]).

Discussion

The present study of community-living older adults did not find that pain severity or interference is associated in any consistent way with poorer cognitive performance. We examined a number of cognitive domains, and after multivariable adjustment, there was a modest association between pain interference and the cognitive measures of memory and general cognitive function. Several associations between pain and cognitive performance were diminished after adjusting for demographic and health measures.

These results provide modest support for the hypothesis that chronic pain may in effect be competing with cognitive task performance. Associations between pain and domains of executive function and memory attenuated when we adjusted for a measure of attention. Eccleston and colleagues proposed in the cognitive-affective theory, that the pain experience demands attention and that this takes precedence over other attention-demanding cognitive processes[22]. Alternatively, in a demonstration of the competing effects of pain on the brain, it is reported that the distraction of demanding cognitive tasks led to reduced pain intensity and reduced activation of multiple pain-related brain areas in healthy young and middle aged adults[48]. Thus, it may be that some older persons who have chronic pain are unable to draw their attention away from their pain and thereby have difficulty performing cognitive tasks while others are able to use distraction to manage their pain. For some, the attentional demands of pain may have a cumulative effect on cognitive functioning, leading to more chronic deterioration of cognitive functioning over time.

In addition to the attention theory described above, human brain studies show that brain regions are involved in both chronic pain and selective cognitive functions and may therefore interact. For example, Apkarian and colleagues showed that the prefrontal cortex (PFC) is involved in chronic pain[49]. The PFC is crucial for many higher brain functions such as representation and execution of actions, goal-oriented behaviour and inhibitory control[50-53]. The orbitofrontal cortex, also involved in chronic pain, links multiple brain regions responsible

for distinct emotional assessments and memory[54-57]. Similarly, a small neuroimaging pilot study showed that smaller hippocampal volumes were associated with more severe acute and chronic pain in healthy elderly adults[58]. Shrinkage of the hippocampus negatively affects various aspects of memory[59-62]. We also found that older adults who reported more severe pain or more pain interference had poorer performance on memory tests and measures of executive functioning compared to elders with none or less pain.

Consistent with our findings from models 1 and 2, other studies involving young and middle-aged chronic pain patients have reported associations between pain and cognitive performance[21,63]. These relationships were particularly evident in the areas of attentional capacity, psychomotor speed and processing speed[21]. A review of clinical and preclinical research on the effect of pain on cognitive functioning suggested that chronic pain influences multiple cognitive domains including memory, attention, executive functioning and speed. These chronic pain conditions included musculoskeletal pain, neuropathic pain and fibromyalgia[64]. Weiner and colleagues found that, cross-sectionally, older adults with chronic low back pain had poorer performance than those without pain, on tests of immediate and delayed memory, learning and mental flexibility[15]. However, they did not report on other sites of pain or global pain characteristics. In addition, other studies have found a relationship between chronic pain and domains of emotional decision making tasks and memory in adult chronic pain patients[16,20]. There was also an association found between pain intensity and diminished mental flexibility in community dwelling older adults who recently started treatment at a pain clinic[19]. However, similar to our study, the association diminished after adjustment for medication, depression, and other factors.

An important aspect of our study is that we used two different global measures of pain, capturing different aspects of the pain experience, pain severity versus interference. Pain interference with daily activities, an indicator of disabling aspects of pain, was most consistently associated with poorer cognitive performance. The accumulating evidence about the link between cognitive and physical function in aging suggests a complex bidirectional or possibly concurrent relationship [65]. It may be that when the experience of pain limits function, it could involve greater cognitive burden as well. Or, alternatively, when pain contributes to cognitive difficulty, it may indirectly contribute to, or exacerbate physical difficulties. Teasing out this relationship through future research will have important implications for treatment.

When interpreting our results, it is important to keep in mind that there is a strong dependence across cognitive domains. Also, most of the cognitive tests used in this study require attentional resources as well as other cognitive functions (e.g. Trail Making Test [32]). Therefore it can be hard to tease out the relationships between measures of pain and

specific cognitive domains. The results of our additional analyses to control for the impact of attentional demands on the observed pain-cognition associations were consistent with Eccleston's theory mentioned above[22]. In other words, the observed relationships between pain and cognitive performance were in part explained by the effect of pain on attentional resources. However, these additional findings could also be due to other unmeasured cognitive influences on the test scores, for example, on the TMT A.

In our study, participants who had more education also reported less severe pain and less pain interference. This has rarely been studied and warrants further consideration because of the clinical implications of this possible disparity. Also, it is well established that educational level influences neuropsychological performance [66-69]. Thus, education was a potential confounder and was included in our analyses. The strong relationship between education and cognitive functioning is complex. A number of studies have observed varying patterns in the associations between education level, neuropsychological test performance and cognitive decline[47,70-72]. While education bias may exist among the instruments, the preponderance of the evidence indicates a strong association between education level and cognitive function [73]. However, more recent longitudinal evidence has not found differences according to education in the rate of cognitive decline with aging[74,75]. Although the observed associations in our study between pain and cognitive function were independent of education, further study is warranted including longitudinal investigations to determine whether chronic pain may influence the rate of cognitive decline with aging.

Our study has several strengths. Pain was associated with decreased cognitive functioning in prior studies of small sample size. However, to our knowledge this is the first study to assess poorer cognitive performance associated with pain in a large population-based sample of community-living older adults. Furthermore, we used multiple global pain measures in contrast to other studies that often targeted single sites of pain or single domains such as pain intensity or chronic low back pain[15,19]. Also, we used a relatively large battery of neuropsychological tests covering multiple cognitive domains.

Our study also had some potential limitations. First, we examined cross-sectional relationships and did not examine changes in pain or cognitive performance over time. We do not know whether these associations varied or would remain constant. In addition to temporality, we cannot confirm directionality of the observed relationships because of the cross-sectional design. It is conceivable that older adults who experience brain changes may be more vulnerable to pain. This is a consideration for future longitudinal investigation.

Also, individuals with significant cognitive impairment (MMSE <18) were excluded from the MOBILIZE Boston cohort. Therefore our results cannot be generalized to elderly persons with moderate to severe cognitive impairment. Older adults with dementia may have other ways of expressing their pain compared to those without dementia[76]. In elderly people with cognitive impairment, challenges in pain assessment and inconsistent findings have been inconclusive regarding relationships between pain intensity and cognitive function[77].

A number of factors influenced the pain-cognitive function relationship that we observed initially. The addition of depression to the adjustments had a substantial impact on the results. Depression may be on the causal pathway between pain and cognitive function. We know from previous work that depression and pain are co-occurring chronic conditions[78]. Among other possible confounders of the pain-cognition association, medications may contribute to cognitive changes, especially in the elderly because of age-related changes in pharmacokinetics, neurotransmitters and the effects of multiple concurrent medications[79]. In our study, the number of analgesics including opioids was not a confounder in the relationship between pain and cognitive functioning. Additional adjustment for chronic conditions and psychiatric medication resulted in attenuation of the effect. We looked at these factors individually and the only measures that substantially altered the observed associations were education, race, and depression.

Given our mixed results about the effect of pain on cognitive functioning, it may be important to pay attention to both pain and cognitive functioning in older adults who live with pain. Factors such as depression and medication may contribute to cognitive problems experienced by older adults living with pain. Cognitive rehabilitation programs have been shown to be effective in older adults to improve function and mood[80,81]. These may prove to be well-suited for older adults living with chronic pain, however, this question remains to be addressed. In addition, since under-treatment of chronic pain is a common problem in older adults in the community[82], chronic pain should be carefully and effectively managed by patients and healthcare providers to reduce risks related to chronic pain and improve quality of life.

In conclusion, our findings present a somewhat mixed picture of the potential impact of pain on cognitive performance in older adults. Pain may result in difficulties in performing cognitive tests and pain may possibly have a cumulative impact over time. Future research is needed to evaluate the effect of pain on cognitive functioning longitudinally and determine whether structural changes in the brain are present and perhaps responsible for changes in cognitive functioning related to chronic pain. In addition, selected populations of older adults may be more vulnerable than others to the cognitive effects of pain. Subsequently, it will be important to look at short and long term pain control interventions for their impact on cognitive functioning in older adults with pain.

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CHAPTER 3

MEASURING ATTENTION IN VERY OLD ADULTS USING THE TEST OF EVERYDAY ATTENTION

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Abstract

Background: There is a need for validated measures of attention for use in longitudinal studies of older populations.

Methods: We studied 249 participants aged 80 to 101 years using the sixth-year follow-up assessment of the population-based MOBILIZE Boston Study. Four subscales of the Test of Everyday Attention (TEA) were included, measuring attention switching, selective, sustained and divided attention and a neuropsychological battery including validated measures of multiple cognitive domains measuring attention, executive functioning and memory. The TEA previously has not been validated in persons aged 80 and older.

Results: Among participants who completed the TEA, scores on other attentional measures strongly correlate with TEA domains (R=.60-.70). Proportions of participants with incomplete TEA subscales ranged from 8% (selective attention) to 19% (attentional switching). Reasons for not completing TEA tests included failure to comprehend test instructions despite repetition and practice.

Conclusion: These results demonstrate the challenges and potential value of the Test of Everyday Attention in studies of very old populations.

Introduction

The concept of attention refers to a person's information processing capacity [1,2]. Performing tasks that require more attention than available will result in reduced performance on those tasks. The Test of Everyday Attention (1994, 1996) (TEA) was developed to measure attention performance in persons with attentional deficits[3]. The TEA has been validated in persons aged 18 to 80 years old, but not in the very old (> 80 years old), who are most vulnerable to diminished cognitive functioning.

The TEA is strongly based on Posner and Petersen's neuro-anatomical model of attention[4]. They propose that attention is fractioned in at least three different systems with all distinct neuro-anatomical bases: (1) a selection system to select relevant processes or stimuli and to inhibit irrelevant ones; (2) a vigilance system responsible for maintaining preparedness in the absence of external signs; and (3) the orientation system to engage and disengage attention in space, e.g., to focus and to take attention away. The first two systems are assessed in the TEA. The test measures different aspects of the selection system, namely divided attention and attention switching[5]. Sustained attention is part of the second system and reflects vigilance[4,6].

Despite the important role of attentional capacity in the elderly, there are few tests to measure attention, specifically multiple domains of attention, in very old adults. In addition, the TEA is based largely on everyday materials, which is useful to identify an individual's attentional problems in real life circumstances. The validation of the Test of Everyday Attention was limited to persons aged 80 and younger and there are no published studies concerning the suitability of the TEA in very old adults. Validated measures of attention are needed in order to measure changes in the attentional domain and to understand their impact in very old adults. The number of people living to very old ages is steadily increasing; from 2000 to 2010, the US population aged 80 and older increased from 7,000,000 to over 9,000,000, a trend that is expected to accelerate in coming decades with the aging of the Baby Boom generation[7]. Therefore, the purpose of this study was evaluating use of the TEA in persons aged 80 and older living in the community.

Methods

The MOBILIZE (Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly) Boston Study (MBS), is a longitudinal population-based study of older adults living in the community in the Boston area. Baseline assessments took place from 2005 to 2008 [8]. Initial eligibility criteria included aged 70 years and older, and able to communicate

in English and walk independently. Moderate or severe cognitive impairment, measured as a score less than 18 on the Mini Mental State Examination (MMSE) was an exclusion criterion[9,10]. The third assessment wave, referred to as MOBILIZE Boston II (MBS II), took place approximately six years from baseline (2011-2015) and included the TEA and a number of other neuropsychological tests. Eligible participants included those who were still residing in the Boston area community and could walk without personal assistance. Participants who experienced severe health deterioration or relocated to a nursing facility were excluded. The current analysis included 249 persons aged 80 and older who completed the MBS II clinic or home visit assessments. A small number (n=39) could not come to the clinic for their assessment and instead completed the neuropsychological assessment in a home visit. The tests were administered by an experienced research assistant trained in the testing protocol by a neuropsychologist with expertise in administering the TEA and the other neuropsychological tests in older and chronically ill adults. Participants signed informed consent at the start of the assessment visit. The Institutional Review Boards of the Hebrew Senior Life and University of Massachusetts Boston approved all procedures and methods. A detailed description of the original MBS design and methods is described elsewhere[8].

Measurements

This cross-sectional study used data from the MBS baseline interview, including sociodemographic characteristics and new assessment data from the MBS II that included health characteristics, the TEA subscales, and the neuropsychological battery.

Sociodemographic and health characteristics

Sociodemographics including age, gender, race, and educational level were assessed at the MBS baseline home interview[8]. Education level was represented by two categories: high school or less (< 12 years of education) and college attendance or graduate school (≥ 12 years of education). Health characteristics include vision, hearing difficulties and self-rated health. In the MBS II assessment, distant vision was assessed using the Good-Lite Chart light box with letter charts, which participants had to read at a 10-foot text distance[11]. Poor vision was defined as the lowest performing quartile. Participants were asked if they had a hearing problem (yes/no) during the interview. Self-rated health was measured on a 5-point scale and dichotomized into fair/poor and good/very good/excellent self-rated health.

Test of Everyday Attention

We measured attention using the TEA, developed by Robertson, Ward Ridgeway, and Nimmo-Smith[3]. The TEA provides a comprehensive assessment of attention measuring multiple domains in adults and was standardized for persons aged 18 to 80 years in a group of British volunteers (Robertson et al., 1996). The test has high test-retest reliability

across different ages and performs well across cultural groups[3,12]. The TEA is based on an imaginary vacation trip to Philadelphia, PA (USA). For this study, we used four subscales of the TEA: Visual Elevator (attentional switching), Map Search (visual selective attention), Telephone Search (selective attention), and the Telephone Search While Counting with dual task (sustained and divided attention). After piloting the TEA with a small number of very old volunteers, the instructions for some of the TEA subscales were modified slightly to make them as simple and clear as possible for American study participants. For instance, in the TEA manual, the instructions for the Map Search were as follows: "*The symbol here shows where gas stations can be found in the Philadelphia area. There are many symbols like this on the map*". Instead of these sentences, we instructed the participants "*This is the symbol that you will be asked to find on a map of Philadelphia. The symbol will be much smaller than this on the map.*" Practice sessions were provided according to the TEA testing guidelines. To accommodate vision and hearing problems, participants were offered magnifying glasses and use of an audio amplifier with headphones before each of the tests.

Attention switching

The Visual Elevator Test is a self-paced task where participants are asked to imagine that they are in an elevator and need to count up and down according to a series of large bold arrows that pointed upward or downwards, shown on display cards. The accuracy score was based on how many correct final floor numbers the participant achieves out of the 10 hypothetical elevator rides shown. The timing score was calculated by counting the time taken for the correctly performed switches (where the elevator switches a number of times going up or down). The Visual Elevator Test measures attentional switching and mental flexibility[3].

Selective attention

As mentioned earlier, the Map Search is a timed visual search task where participants are asked to search for and circle gas pump symbols on a busy colored map of the Philadelphia area. There are also other symbols on the map such as restaurant symbols, with 80 items of each. The total score is calculated according to the number of gas pump symbols circled within 2 minutes.

In the Telephone Search Test, participants are asked to look for matching symbols beside telephone numbers while they are searching a list of plumbers in a simulated telephone directory. The average time-per-target score is calculated by dividing the total time by the number of correctly detected symbols.

Sustained attention
The Telephone Search While Counting Test resembles the previous test. Participants are additionally asked to count a number of series of audio tones presented by a tape recorder. The average time per correctly identified symbols, again, was calculated.

Divided attention
To obtain a measure of divided attention (dual task decrement score), the time-per-target score from the prior Telephone Search task is subtracted from the time per target score weighted for accuracy of tone counting.

Neuropsychological measures
The neuropsychological battery measured a broad range of cognitive functioning including attentional capacity, executive functioning and memory.

In addition to the TEA, the other test of the attentional domain was the Trailmaking Test (TMT) Part A. The TMT Part A requires the participant to connect number targets on a paper in sequential order using a pencil (e.g., 1-2-3-4) [13,14].

The domain of executive functioning includes the TMT Part B, TMT Delta, Clock-in-the-Box Test (CIB) and the Letter fluency Test (F, A, S words). The Trail Making Test Part B requires the individual to connect both number and letter targets in an alternating sequence (e.g., 1-A-2-B-3-C)[13,14]. The difference score between Part A and Part B resulted in TMT Delta, calculated to control for information-processing speed and motor function and is used in other studies to measure executive functioning[15-17]. The CIB requires the participant to read written instructions and to execute those instructions by drawing a clock and setting the clock to the correct time[18,19].

Verbal fluency was tested with three phonemic fluency tasks, where participants are asked to name as many words as possible, beginning with the given letters F, A, and S for 60 seconds for each letter[13].

The Hopkins Verbal Learning Test (HVLT) was used to assess memory. It contains a 12-item word list learning test including immediate recall, delayed recall and a 24-item word recognition test[20]. The MMSE is a short multidimensional assessment instrument, providing information about general cognitive function, also largely in the memory domain [10].

Statistical analysis

Completion of the TEA battery was examined according to demographic and health characteristics. Mantel-Haenzel chi-square tests (1 *df*) were used to test group differences for ordinal variables. For categorical variables, overall chi-square tests were used.

Second, the TEA subscale scores were assessed along with the percentage of participants unable to complete the test. In addition, the reasons for not completing TEA subscales were reported (where only one reason per subscale could be identified). Pearson correlation coefficients were calculated to assess the association between the TEA subscales and the neuropsychological test battery components. We interpreted correlations of R (rho) ≥ .50 as strong correlations and R = .30 - .49 as moderate correlations[21]. All analyses were performed with SPSS v21.0 (IBM Corp., Armonk, NY).

Because we did not use all original components of the TEA, we were not able to replicate the original factor structure of the TEA [3], and accordingly factor analysis was not included in our analyses.

Results

Study Sample Characteristics

Of the initial 328 participants from the original MBS cohort who would be aged 80 and older in the new assessment wave, 17 (5%) had died and 8 (2%) refused to participate. Another 53 persons (16%) were excluded because of severe health deterioration or relocation to a nursing facility or out of the Boston area. Only 1 person had a missing record. This resulted in a final study sample of 249 participants aged 80 to 101 years.

Participants aged 80 years and older in the MBSII assessment wave had a mean age of 87 years (SD=4, range 80 to 101) with 166 women (67%) and 83 men (33%), similar to the original gender distribution of the MBS cohort. A total of 67 (27%) of the 249 participants had incomplete TEAs, meaning they were missing at least one subscale. However, 90% of participants were able to complete at least three of the four tests, 94% completed 2 or more tests and 96% completed at least one test.

Older adults with an incomplete TEA were more likely to have fewer years of education, to be African-American, to have fair or poor self-rated health and to have hearing problems, compared to people who completed the four TEA subscales (Table 1).

Table 1. Completion of the TEA according to demographic and health characteristics in adults aged 80 years and older, MOBILIZE Boston Study II

Characteristics	Completed TEA (n=182) (%)	Incomplete TEA (n= 67) (%)	p value*
Age groups			
80-89 years	78	70	.24
90-102 years	23	30	
Women	65	70	.48
Education			
High school or less	22	42	.002
Attended college	78	58	
Race			
White	86	69	.006
Black	10	25	
Other	4	6	
Fair/poor self-rated health[a]	7	19	.005
Hearing problem[b]	57	74	.017
Vision problem[c]	22	27	.42
Cognition (MMSE<23)	17	63	≤.001

TEA: Test of Everyday Attention; MOBILIZE: Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly.

* Mantel -Haenzel chi-square test (1 *df*), except for race comparisons, which used chi- square test for overall differences (2 *df*).

[a] Self-reported health (fair/poor vs. good/very good/excellent).

[b] Self-reported hearing problem (yes/no).

[c] Poor vision was defined as the lowest performing quartile.

TEA subscales

The distributions of the TEA subscales, including the percentages of participants unable to complete each subscale, are presented in Table 2. Proportions of participants with missing TEA subscales ranged from 8% on the Map Search up to 19% on the Visual Elevator Test. In general, reasons for not completing TEA subscales had to do with failure to comprehend test instructions despite repetition and practice. Most of these people had evidence of possible cognitive difficulties (MMSE score < 23), for example, 69% of those who did not complete the Visual Elevator test had low MMSE scores. Also vision problems played a role in not completing tests, mainly on the Map Search test (15 out of 19 missing tests). Other participants did not attempt the test or refused, resulting in missing data, particularly on the Telephone Search While Counting test (10 out of 31 participants with missing tests). The reasons for not completing the tests are displayed in Table 3.

Table 2. TEA Subscale Scores and Percent Unable to Complete Test

Subscale	Mean (SD)	Median	Range	Incomplete
Visual Elevator[a]	4.67 (1.80)	4.20	2.20 ; 18.20	48 (19%)
Map Search[b]	32.25 (15.58)	32.00	.00 ; 67.00	19 (8%)
Telephone Search[c]	5.54 (3.20)	4.60	2.50 ; 26.10	22 (9%)
Telephone w/ Counting[d]	7.03 (4.97)	5.40	2.80 ; 40.40	31 (12%)
Dual task decrement score	4.90 (9.54)	1.75	-3.10 ; 57.20	45 (18%)

TEA: Test of Everyday Attention.

[a] Timing score, counting the time for correct switches (/time per switch).

[b] Number detected in 2 minutes.

[c] Time per target.

[d] Time per correctly identified symbol.

Table 3. Reasons for not completing TEA subscales

Reason not completed	Visual Elevator N (% miss)	Map Search N (% miss)	Telephone Search N (% miss)	Telephone w/ Counting N (% miss)
Vision problem	7 (15%)	15 (79%)	12 (55%)	6 (19%) [a]
Cognitive problem[b]	33 (69%)	4 (21%)	6 (27%)	15 (49%)
Unable to do	4 (8%)	-	-	
No attempt/ refused	4 (8%)	-	4 (18%)	10 (32%)
Total (N)	48	19	22	31

TEA: Test of Everyday Attention.

[a] Includes three participants with a hearing problem.

[b] Reported by the interviewer or by a MMSE score <23.

There were differences in demographic and health factors associated with selected incomplete tests. For example, less education and African-American race were associated with missing data only in the attention switching task. Poor self-rated health, and hearing and vision problems were associated with inability to complete the Map and Telephone Search Tests (selective attention) (Data not shown).

Correlations

Among participants who completed the TEA, scores on the Trail Making A Test correlated most strongly with several TEA domains, specifically within the domains of attention switching, selective and sustained attention (R= .60-.70, Table 4). The correlation was moderate between

Trail Making A and divided attention (dual task decrement) (R = .41) and selective attention (Map Search) (R = -.49). TMT B was moderately correlated with sustained attention and attention switching. Weakest correlations were observed between the TEA subscales and HVLT tests of recall and recognition.

Table 4. Correlation between TEA subscale scores and neuropsychological tests

Neuropsychological test	Visual Elevator	Map Search	Telephone Search	Telephone w/ Counting	Dual task decrement
Trails A	.60**	-.49**	.64**	.70**	.41**
Trails B	.49**	-.51**	.55**	.46**	.20**
Trails B-A Delta	.33**	-.41**	.45**	.32**	.06
Clock-in-a-box	-.41**	.35**	-.36**	-.39**	-.34**
F, A, and S words	-.33**	.34**	-.40**	-.43**	-.31**
HVLT: immediate recall	-.17*	.37**	-.33**	-.37**	-.24**
HVLT: delayed recall	-.18**	.36**	-.31**	-.31**	-.26**
HVLT: recognition	-.13	.25**	-0.34**	-.30**	-.22**
MMSE	-.37**	.39**	-.45**	-.48**	-.37**

TEA: Test of Everyday Attention; HVLT: Hopkins Verbal Learning Test; MMSE: Mini Mental State Examination.

* Pearson correlation coefficient, p value significant at the .05 level.

** Significant at the .01 level.

Discussion

The results of this study show that in community-living adults aged 80 years and older, the TEA is a valuable measure of attentional resources. The TEA subscales were significantly correlated with another neuropsychological test that measures attention (TMT A). In general, this population-based sample of very old adults was able to complete most of the TEA subscales. The Visual Elevator Test, which measures the domain of attentional switching, was the most challenging test for these older participants, as evidenced by the proportion of incomplete tests related to difficulties in understanding the instructions or in completing the practice test.

The growing recognition of the importance of dual task performance in older adults requires validated tools to measure the attentional domain. Previous studies have shown that attention-demanding 'dual tasks' affect the gait pattern. Older adults who performed a second task while they walked showed reduced gait speed[22-24]. In addition,

the consistency of the gait pattern (gait variability) was altered in idiopathic elderly fallers and patients with Parkinson's disease[23,25], which has been associated with increased fall risk[23,26,27]. We showed that most very old adults in our study population were able to perform the cognitive 'dual task' of the TEA's subscale, i.e., Telephone Searching While Counting.

Our findings are consistent with the original TEA validation, where Robertson and colleagues also found a correlation between the Telephone Search Test (time per target) and Trails B (r= .63) in normal adults aged 18 to 80 years. In a factor analysis, the authors reported that the Trails B loaded on the same factor as Map Search and the Telephone Search Test, namely 'visual selective attention/speed'[3]. Notably, in our study, the TEA was strongly correlated with the Trail Making Test part A, which also measures attention. However, the moderate correlations between several subscales of the TEA and the TMT B and TMT Delta, MMSE, CIB, and Letter Fluency Test may indicate either that some TEA subscales also involve executive functioning or, these other neuropsychological tests also are measuring attentional abilities (e.g., several items on the MMSE require attentional skills). In those TEA subscales, reaction time also may play an important role, which was described previously[28].

Robertson and colleagues described several possible constraints on the validity of the TEA, such as vision, verbal intelligence and various clinical syndromes. In their study, the TEA subscales were not mainly affected by hearing. In addition, they excluded participants with peripheral vision problems who reported difficulty in detecting the symbols on the Map Search Test. Another possible constraint was intelligence. In their study, the Visual Elevator Test was the only test with a partial correlation coefficient exceeding .3, reporting the correlation between the TEA subtest and the The National Adult Reading Test (NART) IQ score (adjusted for age). Robertson and colleagues, therefore, suggest that participants with intelligence below the average and a Visual Elevator score just below the average score should not be seen as an impaired performance on the attentional domain[3]. In this study, reasons for not completing the TEA subscales mainly had to do with failure to comprehend test instructions despite repetition and practice. Approximately one-fifth of older adults were unable to complete the Visual Elevator Test, which is known to be weakly associated with intelligence. It should be noted that the MBS cohort comprises a relatively highly educated cohort of elders, reflecting the demographics of Boston in general. Additionally, it is reflecting those older adults who were most likely to be eligible and interested in participating in this longitudinal study[8]. However, two-thirds of the participants who did not complete the Visual Elevator Test scored below the standard MMSE cut-off point for dementia screening (score below 23), which may explain the

high proportion of incomplete tests. On the other hand, cognitive problems played only a minor role in failure to complete the other TEA subscales, suggesting that the Visual Elevator Test was the most cognitively challenging for this population. It may be that attentional switching is particularly sensitive to age-associated changes, consistent with reported age-related decrements in performance of complex tasks that draw on executive functioning[29]. Moreover, higher education does not protect against age-related decrements in attentional switching[30]. As previously mentioned, although our sample was population-based, MBS participants had more years of education than the general population of older adults. It is likely that we would have had more incomplete tests in a sample with less education.

Similar to Robertson and colleagues' original TEA study, vision problems were sometimes recorded in the MBS II as a reason for not completing the test despite accommodations using magnifying glasses[3]. However, hearing difficulties were not recorded by the interviewers in our study as a main reason for not completing any of the TEA subscales. Participants were able to hear the given instructions and hear the tones in the Telephone While Counting Test, with the exception of only three participants. These participants were already unable to do the testing because of vision problems. Interviewers adjusted the volume of the tones or used an amplifier with headphones when needed. However, people who reported having hearing problems during the health interview were more likely to have an incomplete TEA.

Compared to Robertson's study, we did not examine the TEA in various clinical syndromes, such as stroke, Alzheimer's disease or progressive supranuclear palsy. The MBS initial eligibility criteria excluded persons with moderate or severe dementing illness and those with serious mobility problems, though it is possible that some participants may have mild cognitive impairment. Our findings suggest that some subscales of the TEA, such as the Visual Elevator Test, would not be feasible for subgroups of older adults with serious cognitive impairments.

Overall, our results suggest that some minor modifications to the tests might reduce the missing data in this very old population. First of all, the arrows on the Visual Elevator test could be enlarged for visually impaired persons. Also, the Visual Elevator tasks could be portrayed in one long wide sheet to avoid the line wrapping that created confusion for several participants. Because participants often did not grasp the idea of an elevator going up and down, it may be that this concept is too abstract and other tests of attentional switching may be needed to capture the full range of functioning in this domain. In general, the study staff reported that participants were fatigued by the lengthy instructions for the TEA and might understand the test better

if the introduction was abbreviated. Instead, older adults may perform better on the test if the instructions focused only on the most practical information needed to guide them in performing the tests.

Our study has several strengths, including the substantial sample size of a very old population-based cohort. Key to the current study, we collected specific information about reasons for incomplete tests. Furthermore, we used an attention test covering multiple attentional domains accompanied by an extensive neuropsychological battery.

Our analysis was limited in that we could not fully test convergent validity because we included only some subscales of TEA. We needed to limit subject burden given the advanced age of our participants because the TEA was adminstered within a large battery of physical and cognitive tests. However, we found strong correlations between the Trail Making A score and three out of five TEA subscale scores, and moderate correlations with the other two TEA scores. Trail Making Part B was the only other test showing strong correlations with TEA domains (two out of five subscale scores). A number of the other neuropsychological tests were moderately correlated with the TEA subscales, reflecting the attentional demands of many of these standard cognitive tests in this old population. Using the truncated set of TEA subscales, we could not perform a factor analysis comparable to the original TEA validation, as described previously. However, the TEA has shown good validity and test-retest reliability in persons aged 18-80 years old. Robertson and colleagues generally showed good reliability for 1-week test-retest on TEA Versions A and B in a sample of 154 volunteers and with Versions B and C after another week for a subsample (n=39) of the larger group[3]. Further research is needed to assess test-retest reliability in the population over age 80 years.

In conclusion, these results demonstrate the feasibility and potential value of the TEA for measuring multiple domains of attention in most very old adults. Nevertheless, future research is needed to determine whether adaptations of the test will reduce missing data and make the test more suitable for older persons across a broader range of education and cognitive functioning.

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CHAPTER 4

CHRONIC PAIN AND ATTENTION IN OLDER ADULTS LIVING IN THE COMMUNITY

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Abstract

Background: Maintenance of optimal cognitive functioning during aging is essential for almost every aspect of independent living. Chronic pain is a frequently observed problem in older adults that may interfere with cognitive functioning, especially in the domain of attentional capacity in the elderly. The purpose of this study was to examine the cross-sectional relationship between chronic pain and complex attention in a population of community-living older adults.

Design: Prospective cohort study, cross-sectional.

Setting: Population based Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly of Boston Study II (MOBILIZE Boston Study).

Participants: 354 participants aged 71 to 101 years old.

Measurements: Chronic pain was measured using the pain severity and interference subscales of the Brief Pain Inventory. Four subscales of the Test of Everyday Attention (TEA) were used to measure domains of attention switching, selective, sustained, and divided attention.

Results: Before and after multivariable adjustment, pain severity was associated with poorer scores in measures of selective and sustained attention. Pain interference scores also were significantly inversely associated with selective attention.

Conclusion: The results of this study show that chronic pain is associated with poorer performance in the domains of selective and sustained attention in community-dwelling older adults. Further research is needed to determine whether effective pain management could lead to improved attentional performance in older adults. Older adults who live with chronic pain, often undertreated, are potentially at increased risk for cognitive difficulties and related functional consequences.

Introduction

Maintenance of intact cognitive functioning is essential, especially in advancing age, to maintain mobility and independent functioning of daily activities [1-3]. Impaired cognitive functioning is a risk factor for physical disability, hospitalization and death [4,5]. Decline of cognitive functioning also makes older adults more susceptible to other problems threatening functional independence such as falls and frailty [6,7].

Rates of cognitive decline in aging vary with cognitive abilities and among different people [8]. Several factors can influence the relationship between cognition and aging, including chronic pain. Our previous research showing a modest cross-sectional relationship between pain and cognitive function suggests that chronic pain may compete with the performance of cognitive tasks [9]. Eccleston and colleagues proposed that pain demands attention and that pain will emerge over other demands for attention [10]. It has also been suggested in healthy young and middle aged adults that attention-demanding cognitive tasks can also be used to self-manage the pain, leading to reduced pain intensity [11].

Attention is defined as a person's information processing capacity [12,13]. Beyond the hearing and vision changes that impact perceptual abilities, basic auditory and visual attention typically remain intact with age. In contrast, when greater demands are placed on attention, age-related decrements are commonly observed. These complex attentional abilities include: shifting attention between stimuli, sustaining attention over periods of time and selective attention in which specific stimuli are identified for processing and other stimuli ignored [14,15].

The high prevalence of chronic pain, coupled with heightened vulnerability to cognitive problems in this older population, points to an urgent need for research to understand the chronic pain-attention relationship. Therefore, we investigated whether chronic pain is associated with poorer performance on tests of complex attention in older adults. We hypothesized that older adults experiencing the most pain in terms of severity and pain interference with activities will have poorer cognitive performance on the attentional domain compared to those without pain.

Methods

The population-based cohort for the Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly of Boston Study (MOBILIZE Boston Study, MBS) was recruited from 2005 to 2008 in the Boston area. Details of the study were published previously [16]. Briefly, 765 adults aged 70 years and older, and eligible spouses aged 65

and older were enrolled. Eligibity required communication in English and ability to walk across a small room without personal assistance. Persons were excluded for diagnosis of a terminal illness or evidence of moderate to severe cognitive impairment assessed as Mini Mental State Exam (MMSE) score of 17 or lower [17,18]. The current wave of the study, referred to as the MBSII, consented 354 participants who were continuing to live in the community and agreed to participate in this new phase of the study from 2012 to 2014, approximately 6 to 8 years following original recruitment (MOBILIZE I). Study protocols were approved by the institutional review boards of Hebrew SeniorLife and the University of Massachusetts Boston.

Measurements

The MBSII assessment consisted of a 45-minute health interview by telephone followed by a 3 hour study clinic visit for a health assessment and physical and cognitive performance. For 43 participants (12.1%) who were unable to come to the study clinic, in-home assessments were conducted.

Test of Everyday Attention

We measured complex attention using the Test for Everyday Attention (TEA) [19], designed to measure attentional abilities during tasks resembling everyday activities. The TEA has been validated in persons aged 18-80 years old [20] and an evaluation of utility and missingness of the TEA in persons aged 80 years and older in the MBSII was published previously [21]. This study included 4 subscales measuring attentional switching, visual selective attention, sustained attention, and divided attention. Following the standardized TEA testing guidelines, participants completed a practice session in advance of each test. For people with vision problems, magnifying glasses were provided; for those with hearing problems, use of an audio amplifier with headphones was offered though none of the participants used it.

Attention switching was measured using the Visual Elevator test, which also measures mental flexibility [20]. The Visual Elevator test is a self-paced task where participants are asked to imagine that they are in an elevator and need to count up and down using a series of cards depicting up and down arrows, representing floors on an elevator. The timing score is calculated to determine the time taken for each correctly performed switch (where the elevator switches a number of times going up or down on each card shown to the participant).

Selective attention was measured using the Map Search test, where participants are shown a map of Philadelphia that includes common symbols representing restaurants, gas stations, and other services. Participants are given 2 minutes to circle as many gas

station symbols as they can find on a large paper copy of the map. The total score is calculated according to the total number of gas pump symbols circled within two minutes with the higher score reflecting better performance (in contrast to the scores of the other domains).

The Telephone Search Test, another *selective attention measure*, uses pages from a telephone book that are modified to include simple geometric symbols besides the names of various businesses. Participants are asked to identify as many correctly matching symbols as they can find as they proceed through the columns on the pages. If they have not completed the task within 4 minutes, the test is ended. The score (time-per-target score) is based on the total time divided by the number of correctly detected symbols.

The Telephone Search While Counting Test measures *sustained attention* and resembles the previous test. Participants additionally are asked to count audio tones from a recording while performing the Telephone Search. The score is based on the average time per correctly identified symbols.

Divided attention was measured using the Dual Task Decrement score. The score was calculated by subtracting the time-per-target score from the prior Telephone Search task from the time per target score weighted for accuracy of tone counting.

Chronic pain

The Brief Pain Inventory (BPI) subscales measured global pain severity and pain interference [22,23]. The BPI has been validated as a measure of chronic non-malignant pain in older adults and shows good reliability (coefficient alphas > 0.70) [24,25]. For the BPI severity subscale, participants are asked to rate their pain, described as pain "you have today that you have experienced for more than just a week or two". For the 4-item severity scale, participants rate their pain in the previous week on a numeric rating scale from 0-10, where 0 reflects 'no pain' and 10 reflects 'severe or excruciating pain, as bad as you can imagine', in terms of pain at its worst, least, on average in the previous week, and at present. The BPI severity score is the average of the 4 ratings.

Using the BPI pain interference subscale, interference in daily activities was rated for general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. Rating for each item was on a 0-10 numeric rating scale, with 0 indicating no pain interference and 10 indicating complete interference; the score was the average of the 7 item ratings.

Sociodemographic and Health Characteristics

We selected sociodemographic and health characteristics that were possible confounders and could potentially interfere with test performance. Sociodemographic characteristics assessed at baseline included age, gender, race and educational level. Education level was assessed as number of years of formal education. Health characteristics assessed in the telephone interview and clinic exam included body mass index (BMI), heart disease (self-reported) and diabetes and depression, assessed by disease algorithms, described previously [16]. Obesity was determined based on body mass index (BMI) of 30 or greater. Following a musculoskeletal assessment using clinical criteria for osteoarthritis of the hand and knee, arthritis was categorized into 4 groups: no arthritis, hand only, knee only and both (hand and knee) [26,27]. Vision was assessed using the Good-Lite Chart light box, where participants were asked to read text at a 10-foot distance [28]. The lowest performing quartile was classified as poor vision. Self-reported hearing difficulties were assessed during the health interview on a binary scale (yes/no). Medications used in the previous 2 weeks were assessed using the brown bag method. Psychiatric medications included anxiolytics, sedatives and hypnotics, antidepressants, and antipsychotics. Analgesic medications include opioid and non-opioid classes as well as medications for neuropathic pain (i.e. gabapentin and pregabalin).

Statistical analysis

Participant characteristics were examined according to BPI pain severity tertiles (none or least pain: BPI severity score <1, mild pain: score 1 to 3.9, and moderate to severe pain: BPI≥4). Similarly, BPI interference scores were grouped into tertiles. Between-group differences according to baseline characteristics were tested using chi-square tests for categorical measures and ANOVA for ordinal and continuous measures.

Attention scores of the TEA subscales were investigated according to BPI pain severity and interference scales. TEA subscale scores were highly skewed and subsequently winsorized at the 99th percentile to control for outliers. We used unadjusted general linear models (GLM) to test potential linear relationships between BPI pain score groupings and TEA scores (dependent variables).

Multiple linear regression modeling was used to investigate relationships between pain measures and TEA subscales. We performed two models, initially adjusting for sociodemographic measures (age, sex, race, education), then extending the model by adding variables that could potentially interfere with the TEA test performance (hand arthritis and vision), heart disease, diabetes, BMI and psychiatric medication use. The magnitude of the effect of chronic pain on attention is expressed in unstandardized regression coefficients.

All analyses were performed with SAS v 9.4 (SAS Institute, Cary, NC).

Results

Study Sample Characteristics

Study participants (n=354) had an average age of 84.5 years (SD=4.7) including approximately two-thirds women (65.8%), similar to the older population of the Boston area. Participants had an average of 14.8 years (SD=2.8) of education and 79.9% were white and 14.4%, African-American. Participants with moderate to severe pain were more likely to have fewer years of education, be female, African-American, have obesity and arthritis, and use analgesics and psychiatric drugs, compared to people with none or mild pain (Table 1).

TEA subscales

Participants with moderate to severe pain severity or interference had poorer performance than those with none or less pain in the domain of selective attention (Telephone Search and Map Search tests; Table 2). After adjustment for age, gender, race and education, pain severity was associated with lower scores on one domain of complex attention; selective attention (Telephone Search: p-value 0.04, Map Search: p value .03; Table 3). In addition, after adjustement for health factors and psychiatric medication use, pain severity was associated with sustained attention (Telephone search while counting, p value .04). Pain interference was inversely associated with the Telephone Search score (p value .03).

Table 1. Demographic and health characteristics according to pain severity clinical cutpoint groups, adults aged 71 and older, MOBILIZE Boston Study II

Characteristics		**None or least pain**	**Mild pain**	**Moderate to severe pain**	**p value***
		(n=126)	**(n=165)**	**(n=63)**	
	Total		**Mean (SD)**		
Age(years)	84.54 (4.72)	84.07 (4.78)	84.78 (4.76)	84.84 (4.47)	.38
Education(years)	14.78 (2.82)	15.30 (2.59)	14.79 (2.61)	13.73 (3.45)	.001
			Percent		
Women	65.82	57.14	68.48	76.19	.02
Race					
White	79.94	79.37	85.45	66.67	
Black	14.41	13.49	10.91	25.40	
Other	5.65	7.14	3.64	7.94	.03
Chronic conditions			Percent		
Obesity (BMI ≥30)	20.62	16.67	18.18	34.92	.01
Arthritis:					
None	68.71	85.83	60.54	54.24	
Knee only	11.04	6.67	14.29	11.86	
Hand only	13.50	7.50	17.69	15.25	
Hand and Knee	6.75	0	7.48	18.64	<.0001
Heart disease	45.19	38.52	47.20	53.33	.13
Diabetes	13.56	12.70	13.33	15.87	.83
Depression	5.65	2.38	7.27	7.94	.14
Psychiatric drugs [a]	20.06	13.49	20.00	33.33	.01
Analgesic drugs [b]	29.10	15.87	27.27	60.32	<.0001
Low vision	22.36	18.49	24.50	25.00	.44
Limited hearing	57.06	59.20	59.51	45.76	.16

[a] Used (anxiolytics, sedatives and hypnotics, antidepressants, and antipsychotics) in the previous two weeks.

[b] Used opioid or non-opiod analgesics in the previous two weeks.

[c] BPI Pain Severity clinical cutpoint groups: none or least pain, 0-0.99; mild pain, 1-3.99; moderate to severe pain, 4-10.

* Chi-square test for categorical variables and ANOVA test for continuous variables significance level at .05.

Table 2: Attention scores according to BPI pain severity clinical cutpoint groups and interference subscales [a] in adults aged 71 and older, MOBILIZE Boston Study II

		BPI Pain Severity [c]			
TEA Subtests [b]		**None or least pain**	**Mild pain**	**Moderate to severe pain**	**p value***
	N	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
Telephone Search Test	335	4.83 (2.34)	5.54 (3.62)	5.87 (3.48)	0.03
Map search	334	38.22 (16.41)	33.54 (15.50)	31.22 (13.75)	0.002
The Telephone Search While Counting Test	309	11.26 (14.22)	9.72 (10.52)	14.31 (19.98)	0.37
Dual task decrement score	306	6.78 (13.43)	4.66 (9.61)	9.26 (18.65)	0.52
Visual elevator	298	4.32 (1.16)	4.58 (1.84)	4.50 (1.35)	0.33
		BPI Interference			
		None or least interference	**Mild interference**	**Moderate to severe interference**	**p value***
	N	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	
Telephone Search Test	335	4.83(2.23)	5.85(3.97)	6.41(4.37)	0.001
Map search	334	37.66(15.53)	31.45(16.02)	29.67(13.77)	0.001
The Telephone Search While Counting Test	309	10.25(12.57)	10.82(12.04)	14.42(20.05)	0.09
Dual task decrement score	306	5.63(11.72)	5.57(11.18)	9.16(18.72)	0.16
Visual elevator	298	4.38(1.43)	4.64(1.81)	4.57(1.52)	0.27

[a] Generalized linear models tested unadjusted associations between BPI clinical cut-points and TEA scores.

[b] TEA subtests, 5 scales: selective attention (Telephone Search Test, Map search), sustained attention (The Telephone Search While Counting Test), divided attention (Dual task decrement score), and attentional switching (Visual elevator test).

For all subscales, lower scores indicate better performance except the Map search.

[c] BPI Pain Severity clinical cutpoint groups: none or least pain, 0-0.99; mild pain, 1-3.99; moderate to severe pain, 4-10.

***** p Value, test for trend (1df) entering pain severity and interference tertiles as ordinal variables in the models.

Table 3. Associations between BPI pain severity and interference scores and attention scores adults aged 71 and older, MOBILIZE Boston Study II

TEA Subtests	Mean (SD)	BPI Pain Severity Score			
		Model 1[a]		Model 2[b]	
		Coefficient	p value	Coefficient	p value
Telephone Search Test	5.34 (3.21)	0.18	.04	0.18	.04
Map search	34.81 (15.72)	-0.98	.03	-0.84	.07
The Telephone Search While Counting Test	11.05 (13.90)	0.77	.06	0.88	.04
Dual task decrement score	6.17 (12.96)	0.65	.10	0.74	.08
Visual elevator	4.47 (1.55)	0.03	.56	0.02	.67
TEA Subtests	**Mean (SD)**	**BPI interference score**			
		Model 1[a]		Model 2[b]	
		Coefficient	p value	Coefficient	p value
Telephone Search Test	5.34 (3.21)	0.19	.03	0.19	.03
Map search	34.81 (15.72)	-0.75	.08	-0.65	.15
The Telephone Search While Counting Test	11.05 (13.90)	0.59	.14	0.52	.23
Dual task decrement score	6.17 (12.96)	0.56	.14	0.49	.23
Visual elevator	4.47 (1.55)	0.01	.92	-0.01	.76

[a] Multiple linear regression models, TEA scores were dependent variables; Model 1 adjusted for age, gender, race, and education.

[b] Model 2 additionally adjusted for vision, hand arthritis, diabetes, heart disease, BMI, and use of psychiatric drugs.

Discussion

This is among the first studies of an older population to examine the possible impact of chronic pain on selected domains of attentional capacity in older adults. The results demonstrate that chronic pain is associated with attentional challenges in community-living older adults. Before and after multivariable adjustment, pain severity was associated with poorer selective and sustained attention, and pain interference also was significantly associated with poorer selective attention.

Our results are in line with earlier clinical studies of adults with chronic pain, where chronic pain was associated with selected cognitive impairments [29-32]. In a previous MBS report, we observed modest associations between pain and other cognitive domains among the

original cohort of 765 participants [9]. In that analysis, MBS partcipants experiencing more severe pain or pain interference performed worse on executive functioning and memory tests, compared to participants with less or no pain. Additionally, pain interference was associated with impaired attentional capacity, measured using the Trailmaking test Part A. However, many of the observed associations attenuated after other factors including chronic conditions, behaviors and psychiatric medication were taken into account. In addition, adjusting for performance in tests of attention diminished the association between pain and general cognitive functioning, supporting the idea that attention may explain previously reported associations between pain and general cognitive decline [9]. The current study findings are not only consistent with previous MBS I results, but suggest that chronic pain in older adults may be particularly detrimental to domains of selective and sustained attention. It is possible that impaired selective attention contributes to previous findings of reduced executive functioning and memory. A previous study also suggested that the influence of pain on memory processes is secondary to the influence of pain on attention rather than primarily on memory [32] . Others have suggested that selective attention plays a role in the executive control aspect of the working memory system [33]. Therefore our findings may not only present new information about the relation between pain and attention, but also may have broader implications for the existing evidence describing associations between pain and other cognitive domains.

No relation was found between pain severity or interference and attentional switching. The absence may be explained in part by the difficulty of the Visual Elevator test for older adults. Our previous work showed that this test was probably the most difficult test for those aged 80 and older, resulting in more incomplete tests (19% of participants had incomplete tests of attentional switching versus 8% on the selective attention tests). We reported previously that 69% of participants with incomplete Visual Elevator tests had low MMSE scores [21]. Nonetheless, additional analysis addressing the problem of missingness using multiple imputation for the Visual Elevator test did not change our findings (data not shown).

A review evaluating the effect of chronic pain on neuropsychological performance identified cognitive impairment among patients with chronic pain irrespective of age, particularly in the domains of attention, processing speed and psychomotor speed [30]. However, the authors suggest that multiple factors, yet to be identified, may mediate or explain the relation between chronic pain and cognitive functioning [30]. Iezzi and colleagues identified that factors such as education, can influence this relationship. They initially observed associations between chronic pain and attention in clinical adult patients [29]. However, after controlling for the effect of education, the assocation was diminished. In our study of very old adults living in the community, the relationship of pain and attention was independent of education.

Our results are consistent with Eccleston's theory that pain demands attention and takes precedence over other attention-demanding cognitive tasks [10]. This effect might be greater for older adults with chronic pain, in part because of distracting effects of pain but also because, with aging, there is reduced ability to handle more than one task at a time [34]. In our study, nearly all participants with chronic pain reported they were experiencing pain on the day of the cognitive testing (data not shown).

Additional evidence can be found by reviewing the brain regions involved in both pain and complex attention. In older adults with chronic back pain, MRI studies reveal losses in brain volumes in the cingulate cortex area, which is involved in the processing of pain and also in attentional challenges [31]. Other imaging studies showed activation of the prefrontal cortex during pain experience as well as during complex attentional processing [35,36]. Therefore, the effect of chronic pain may be related to chronic interruption of current attentional engagement [10]. It is possible that chronic pain may have a cumulative negative effect on cognitive functioning, contributing to cortical reorganization due to brain plasticity. While plasticity is typically viewed as advantageous, in the presence of chronic pain, plasticity may lead to changes in brain morphology, with loss of gray matter volume, such as in the insular cortex, anterior cingulate cortex, and dorsolateral prefrontal cortex [31,37,38]. In a review on pain and cognition, Moriarty and colleagues proposed potential mechanisms involved in pain-related cognitive impairment: division of limited resources in the brain, adverse neuroplastic changes that occur in the brain of chronic pain patients, and neurochemical mediators released during chronic pain [38]. One or more of these mechanisms may have contributed to the associations we observed between chonic pain and attention in the older population.

Older adults who have pain may be particularly vulnerable to impairment in selective attention, which involves not only the selection of appropriate stimuli, but also, the inhibition of distracting stimuli. Poor selective attention is typically associated with the poor inhibition aspect of selective attention. Pain might impair inhibition, when it becomes difficult to ignore it. Participants who had more severe pain generally performed worse than those without pain on other TEA subscales, however the decrements in the other attentional domains were not consistently significant.

This study has some notable strengths, including use of two different global pain measures. Another strength is that the TEA assesses several domains of attention and may provide a more ecologically valid assessment of complex attention compared to the commonly employed clinical measures (e.g., Stroop; Trail Making). Previously we reported that TEA scores correlated with other cognitive tests in the MBS II, and that, in general, very elderly participants were able to complete most of these challenging

attentional tasks, except for the visual elevator test [21]. Lastly, our study is population-based, thus our findings are more representative than other studies involving patient volunteer samples.

Our findings overall of the fully adjusted models are modest. This could be in part due to the sample size or it could be that other factors not accounted for in our analysis could explain the observed associations. Further research is needed to better understand the impact of chronic pain on cognition in older adults. Another limitation of this study was its cross-sectional design. Therefore, we cannot determine the temporality and directionality of the relationship between pain and attention. Longitudinal research on this topic is needed. Also, we were not able to describe the nature and source of the pain. Furthermore, we did not adjust for analgesic use or specifically, opioid use, because use of these medications is strongly associated with pain severity. Thus, we cannot be certain whether the observed associations between pain and attentional deficits are completely independent of medications used for pain management. Another possible limitation is that the TEA is a challenging test, especially in older adults. Our previous report addressed the problem of missingness of the TEA and suggestions for modifications in very old adults [21]. Future studies need to investigate the suggested modifications.

In conclusion, our findings support that chronic pain may compromise complex attention in older adults. There is growing evidence that maintenance of cognitive functioning including attention in older adults is essential to mobility and daily function [1,39]. Also attentional demands for postural control increase with aging as sensory information decreases [12,40]. Thus, decreased attentional capacity in older adults could lead not only to decreased cognitive functioning overall, but also to imbalance, mobility decline and falls. Research is needed on the long term effects of pain on attentional processes and other cognitive functions and mobility with aging. Perhaps most importanty, we need to determine whether improved pain management reduces the attentional burden of pain and its functional consequences in this vulnerable population.

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CHAPTER 5

The effect of pain on major cognitive impairment in older adults

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Abstract

Background: Older adults frequently report pain; cross-sectional studies have shown that pain is associated with worse cognitive function. However, longitudinal studies are lacking.

Methods: We prospectively studied 441 participants without dementia, including 285 with pain, aged 65 years and older, enrolled in the Central Control of Mobility in Aging Study, a prospective cohort study. We analyzed the longitudinal association between pain (Medical Outcomes Study pain severity scale) and major cognitive impairment (Repeatable Battery for the Assessment of Neuropsychological Status and the Trail Making Test Delta) using Cox regression analysis adjusted for age, gender, ethnicity and education.

Results: Over a mean follow-up of 2.75 years (standard deviation = 1.94 years) there was no difference in the risk of developing cognitive impairment between participants with pain and participants without pain. However, among those with pain, risk for developing major memory impairment was higher among those with high levels of pain, compared to those with low levels of pain (adjusted hazard ratio: 3.47, 95% confidence interval: 1.42-8.46). The association with pain and incident impairments in attention or executive function was not significant.

Conclusion: We did not find that pain is associated with incident cognitive impairment in general, but among older adults with pain, a high level of pain is associated with increased risk of developing incident memory impairment.

Perspective: Our study results suggest that high levels of pain may contribute to incident memory impairment. Further research is needed to determine whether a high level of chronic pain is a modifiable risk factor for cognitive impairment in older adults.

Introduction

Pain is a frequently reported problem by older adults. More than 50% of community-dwelling older adults and up to 70% of older adults in residential homes, experience pain, and the prevalence of chronic pain increases with advancing age[1,2]. In older adults chronic pain interferes with daily activities, and has been associated with risk of developing disability[3], risk of falls[4,5], functional impairment and poor self-rated health[6-10].

Chronic pain may also affect cognition in older adults. Previous cross-sectional studies have shown that chronic pain is associated with worse cognitive function in older adults[11,12]. However, the cross-sectional design of these studies limits inferences about temporality of the association between pain and cognition. There is a paucity of studies that assess cognitive functioning longitudinally in patients with pain symptoms. The only longitudinal study to date showed that persistent moderate to severe pain at baseline was associated with accelerated memory decline and increased risk of dementia in a large population-based sample of older adults[13]. The effect of persistent pain on only one cognitive domain (memory) was investigated in this study[13], whereas cross-sectional studies suggest that chronic pain may also have detrimental effects on other cognitive domains such as attention, information processing, executive functions and general cognitive function[11,12,14-16]. Furthermore, the contribution of pain severity to future risk of developing cognitive impairment is not well established.

To address these knowledge gaps regarding the cognitive consequences of pain, we studied older adults participating in a community-based prospective cohort study. Establishing the longitudinal association of pain severity with deterioration of cognitive domains may shed light on a potentially modifiable risk factor for cognitive impairment in aging and open up new avenues of treatment of cognitive impairment. First, we investigated whether presence of pain increases the risk incident cognitive impairment compared to no pain in our study population, as previous studies have established cross-sectional differences in cognition between older adults with and without pain[11,12,16]. Next, we analyzed whether higher levels of pain lead to a higher risk of developing incident cognitive impairment. Building on previous cross-sectional studies[11,12,16], we hypothesized that presence and severity of pain would be associated with risk of developing future cognitive impairments in the domains of attention, executive functioning, and memory.

Methods

The Central Control of Mobility in Aging (CCMA) study is a prospective cohort study of mobility in community-dwelling adults aged 65 years and older living in lower Westchester County, New York. A detailed description of the study design has been published[17]. In brief, potential participants aged 65 and older, identified from population lists of lower Westchester County, were contacted by mail and later by telephone and invited to participate in the study. All potential participants completed a telephone-screening interview to assess study eligibility. Exclusion criteria were inability to speak English, inability to walk independently, presence of dementia (identified by cognitive screening during telephone interview or at consensus case conferences following an in-person visit as described below), progressive neurological diseases or psychiatric disorders severe enough to prevent assessments, major hearing or vision difficulties, patients on hemodialysis, and recent or scheduled medical procedures that may affect mobility. For the purposes of the present analyses, participants with mild cognitive impairment (MCI), motoric cognitive risk syndrome (MCR), or dementia at baseline were excluded from all analyses to minimize false responses or underreporting of pain severity. Cognitive status was diagnosed at consensus case conferences attended by one or more study clinicians and neuropsychologists with access to all clinical and neuropsychological information and any available investigations, and was categorized as normal cognitive functioning, MCI, MCR, and dementia. Current operational definitions for MCI[18,19] and dementia[20] were used. MCR was defined as the presence of cognitive complaints, slow gait, preserved activities of daily living and the absence of dementia, and has been described previously in the CCMA and other cohorts[21,22].

After completing the telephone interview, eligible participants attended two in-person visits at the research center and returned for up to six annual follow-up visits between 2011 and 2017, where they received detailed cognitive, psychological, neuropsychological, and mobility assessments. Participants provided written informed consent prior to enrollment. The study has been approved by the Albert Einstein College of Medicine Institutional Review Board.

Measures

Trained research assistants under the supervision of the study neuropsychologist administered the pain questionnaire and neuropsychological battery. All study assessments were done at baseline and repeated at annual follow-up visits at our research center (Division of Cognitive and Motor Aging, Albert Einstein College of Medicine).

Pain severity (independent variable)

Pain was assessed by the 7-item pain questionnaire from the Medical Outcomes Study (MOS)[23]. The overall reliability for the MOS pain questionnaire is excellent (0.86)[24]. Participants were first asked if they had experienced bodily pain in the past four weeks. If they answered that they had not experienced any bodily pain, the subsequent six questions were skipped. If they answered affirmatively, they were asked the remaining six questions. Pain severity was measured with one item on this MOS questionnaire that uses a 20-point scale to record pain severity. Participants were asked to rate their severity of pain on average over the previous 4 weeks, with responses ranging from 0 ('no pain') to 20 ('pain as bad as you can imagine').

We examined the pain score as both a dichotomous ('no pain': score 0, and 'pain': score 1-20) as well as a continuous measure. In addition, as pain severity is often categorized in clinical practice, we also examined the pain score in quartiles (1. 'no pain' [score = 0]; 2. 'low pain' [score = 1-4]; 3. 'medium pain' [score = 5-8]; 4. 'high pain' [score = 9-20]) and in tertiles (lowest tertile 'low pain' [score = 1-4], middle tertile 'medium pain' [score = 5-8], highest tertile 'high pain' [score = 9-20]) to aid clinical applicability of any findings.

Duration of pain was not assessed by this questionnaire. However, the pain categories were relatively stable. Over a 1-year period, 80.8% of the participants categorized as a high level of pain at baseline, were also in the 'medium' or 'high' pain categories at the next annual visit, and only 13.1% reverted to 'no pain' at the next annual visit.

Cognition (Outcome measure)

Research assistants administered an extensive neuropsychological battery, including assessment of general mental status and other cognitive domains to all participants at the clinic visits. Based on our hypothesis, we selected tests measuring the three cognitive domains that were associated with pain severity cross-sectionally in previous studies[11,12,16]: attention, executive functioning, and memory. We did not include information processing speed as a separate outcome measure, since processing speed is captured in the tests for the other cognitive domains. The Trail Making Test (TMT), for instance, measures a complex cognitive construct, including visual search, scanning, processing speed and mental flexibility, besides executive functioning[25]. The TMT Delta (see description below) is proposed and used as a purer measure of executive functioning[26].

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[27] is a widely used composite neuropsychological test that measures general mental status and various cognitive domains. The RBANS is a valid and reliable tool for detecting cognitive deficits across different age levels and diagnostic groups[28]. The RBANS has a total score and five indices that measure different aspects of cognition

(immediate memory, visuospatial/constructional, language, attention, and delayed memory [recognition and recall after several minutes]). For this study, we selected the attention and delayed memory (delayed recall and recognition of visual and verbal information) indices. All index scores range from 62 to 138; higher scores reflect better performance.

To examine executive functioning, we calculated TMT Delta by subtracting the TMT Part A score from the TMT Part B score. For TMT Part A, participants had to connect number targets sequentially (e.g., 1-2-3-4) as fast as possible, with a maximum completion time of 300 seconds. TMT Part B contains number and letter targets that need to be connected alternately (e.g., 1-A-2-B), also with a maximum time of 300 seconds[29]. TMT Delta is used to control for information processing speed and motor function, and is recognized as a direct measure of executive functioning[26,30-32]. TMT Delta is measured in seconds, with a shorter time reflecting better performance.

Covariates

We selected the following sociodemographic and health variables to include as covariates to account for confounding based on reported associations with pain and cognition in previous studies[12,13]. Sociodemographic characteristics assessed by the research assistants at the baseline interview included age, gender, ethnicity, and years of education. Health characteristics included general health, depressive symptoms, and medications. Physician-diagnosed medical illnesses and medications were reported by participants to the study clinician during the study visits. A general health score (GHS; range = 0-10) was calculated, as previously described[33,34], by summing the following self-reported physician-diagnosed diseases: diabetes, chronic heart failure, arthritis, hypertension, major depression, stroke, Parkinson disease, chronic obstructive lung disease, angina and myocardial infarction. Medical records, when available, were also reviewed to assess accuracy of self-reports of illnesses and medications. Depressive symptoms were measured with the 30-item Geriatric Depression Scale (GDS)[35,36]. Participants were asked to bring in medication bottles, their medication lists, or both to clinic visits. We assessed use of psychiatric medications (yes or no) because of the potential effects on cognitive function, including antidepressants, antipsychotics, benzodiazepines, barbiturates, and other sleep medication. Analgesic use (yes or no) was also assessed, including miscellaneous analgesics; nonsteroidal anti-inflammatory drugs (NSAID's), anti-seizure medication for treatment of neuropathic pain (e.g., gabapentin and pregabalin); and (weak) opioids, including tramadol. Frequency of use of medications was not assessed in our dataset.

Statistical analysis

We examined demographic and health characteristics per dichotomous pain variable ('no pain' versus 'pain' of any severity). Between-group differences were analyzed using analysis of variance (ANOVA) for continuous measures and chi-square tests or Fisher exact test for categorical measures. Cognitive test scores were examined for each dichotomous pain variable.

We first analysed the association between pain (of any severity) and the incidence of major cognitive impairment during follow-up using Cox regression analysis compared with no pain, adjusted for age, gender, ethnicity, and education. The results were reported as hazard ratios (HRs) with 95% confidence intervals (CI). The time to event was from baseline to major cognitive impairment or to final visit. Incident major cognitive impairment was defined dichotomously as a score on a particular test at a follow-up study visit that was 1 standard deviation (SD) or more below the mean score of the study population on the test at baseline. This definition of major cognitive impairment has been used before in our cohort[37]. For the RBANS, cut-offs of 1 and 1.5 SD below the mean of the comparison sample have been used to detect cognitive impairment associated with Alzheimer Disease[38], and a cut-off score of 1 SD below the mean for the Delayed Memory Index was shown to have the best combination of sensitivity and specificity to detect mild cognitive impairment syndrome[39]. Our study sample excluded participants with MCI, MCR, and dementia syndromes at baseline. For the Cox regression analyses, participants with prevalent cognitive impairment on the domain included in the analysis were additionally excluded. Prevalent cognitive impairment was defined as a score of 1 SD below the mean on the individual cognitive domains at baseline.

Next, pain severity was analysed as a predictor, using four categories (no pain [reference group] and low, medium, and high levels of pain). The effect of low, medium, and high levels of pain on cognitive function was analysed using Cox regression analyses, adjusted for age, gender, ethnicity and education, compared to older adults without pain (reference group).

Finally, because the cross-sectional detrimental cognitive effects of pain are well known[11,16], we focused only on older adults with pain. Pain was analyzed as a continuous variable (range = 1-20) and in tertiles (low [reference group], medium, and high levels of pain). The association between pain severity and cognitive impairment was adjusted for age, gender, ethnicity and education (Model 1). We then included additional adjustments for GHS, depressive symptoms, and use of psychiatric medications and analgesics (Model 2). Proportional hazard assumptions of the models were examined analytically and were additionally checked graphically. All analyses were performed using SPSS v. 24 (SPSS Inc., Chicago, IL).

Results

Study population

Of the 590 CCMA participants enrolled between June 2011 and September 2017, 521 had baseline data on pain and cognitive testing completed. Eighty participants were excluded because of presence of dementia (n=7), MCI (n=66) or MCR (n=7), diagnosed at baseline. Of the remaining 441 eligible participants, 285 (64.6%) reported pain (of any severity). Eligible participants were younger ($p < .001$) and had more years of education ($p = .002$) than those excluded. The mean follow-up of the 441 participants was 2.71 years (SD = 1.96, range = 0-6.16 years).

The mean age of the 441 eligible participants was 76.1 years (SD=6.4) with 195 men (44.2%) and 246 women (55.8%). Older adults with pain were more likely to be female, be African-American, and have higher depression scores, more chronic diseases and, and higher use of analgesics than those without pain (Table 1). Twenty-eight (9.8%) participants with pain were receiving one or more psychiatric medications. Forty-one participants (14.4%) with pain were using analgesics, including (weak) opioids (n=9). The source and nature of pain in our ambulatory and relatively healthy population was not ascertained. However, of the participants with pain at baseline, 55.4% (n=158) reported osteoarthritis or degenerative orthopedic problems, 12.6% (n=36) migraine headaches, 11.9% (n=34) peripheral neuropathy, and 5.6% (n=16) spinal stenosis, and no participants were receiving chemotherapy for cancers at baseline.

Table 2 shows mean neuropsychological test scores according to the 'no pain' and the 'pain' groups at baseline. Cross-sectionally, there was no significant difference on cognitive scores between the groups.

Pain severity (including no pain)

Over an average follow-up of 2.75 years (SD = 1.94), 56 (13%) participants developed major cognitive impairment in the domain of attention, 60 (14%) in the domain of executive functioning, and 49(11%) in the memory domain (see Methods for operational definitions).

The sample sizes for the separate Cox models used to study impairments in the three selected domains ranged from 370 to 382 (Table 3), after exclusion of participants with prevalent cognitive impairment on the analysed domain. Compared with the older adults without pain, the adults with pain did not have a higher risk of developing major cognitive impairment in any of the three cognitive domains (Table 3A). Only older adults with the highest level of pain tended to have a higher risk of developing

memory impairment than those without pain, although the effect was not significant (HR adjusted for age, gender, ethnicity, and education = 2.03, 95% CI = .95-4.36, p = .069). There was no association between high levels of pain and incident impairment in the attention (p = .525) or executive function domains (p = .427) (Table 3B).

Table 1. Demographic characteristics according to pain (no/yes) in older adults aged 65 years and older at baseline

Characteristic Mean (SD) or N (%)	Overall sample N=441	Pain at baseline no/yes		p value*
		No pain N=156	Pain N=285	
Age (years)	76.08 (6.39)	76.68 (6.37)	75.76 (6.39)	.149
Gender				.005
Women	246 (55.8%)	73 (46.8%)	173 (60.7%)	
Men	195 (44.2%)	83 (53.2%)	112 (39.3%)	
Ethnicity				.002
White	375 (85.0%)	135 (86.5%)	240 (84.2%)	
Black	52 (11.8%)	11 (7.1%)	41 (14.4%)	
Other	14 (3.2%)	10 (6.4%)	4 (1.4%)	
Education (years)	14.92 (2.97)	14.78 (3.07)	15.00 (2.92)	.462
GDS[a] score (0-30)	4.53 (3.96)	3.67 (3.27)	4.99 (4.22)	.001
GHS [b] (0-10)	1.60 (1.08)	1.31 (0.94)	1.76 (1.12)	≤.001
Psychiatric medication [c]	37 (8.4%)	9 (5.8%)	28 (9.8%)	.142
Analgesics [d]	52 (11.8%)	11 (7.1%)	41 (14.4%)	.022
Analgesic AND psychiatric	10 (2.3%)	3 (1.9%)	7 (2.5%)	.503

* Using ANOVA for continuous variables and the chi-square test or Fisher exact test for categorical variables.

a. Geriatric Depression Scale

b. Global Health Score: sum of diabetes, chronic heart failure, arthritis, hypertension, major depression, stroke, Parkinson disease, chronic obstructive lung disease, angina, and myocardial infarction.

c. Antidepressants, anti-psychotics, benzodiazepines, barbiturates, and sleep medication.

d. Miscellaneous analgesics, NSAIDs, antiseizure (for neuropathic pain: gabapentin and pregabalin), (weak) opioids.

Pain severity (among older adults with pain)

The total sample for studying the threshold effects of pain severity was the 285 participants who reported pain at baseline. Within this group, 35 (12%) participants developed incident cognitive impairment in attention, 38 (13%) on executive functioning, and 31 (11%) on memory over an average follow-up of 2.79 years (SD = 1.96). The sample

size for the separate Cox models used to study impairments in the three selected domains ranged from 243 to 252 (Table 4), after exclusion of participants with prevalent cognitive impairment on the analyzed domain.

Table 2. Cognitive performance according to pain (no/yes) in older adults aged 65 years and older at baseline

Cognitive domain [a]	**Pain No/Yes**		
	No pain N=156	**Pain N=285**	
	Mean (SD)	Mean (SD)	p value*
Attention	101.28 (14.76)	102.53 (13.93)	.377
Executive function	71.97 (45.42)	70.75 (44.44)	.785
Memory	93.94 (10.50)	94.86 (9.58)	.352

* Using the chi-square test or Fisher exact test.

a. Attention: RBANS, range 62-138; Executive function: TMT Delta, range 0-300; Memory: RBANS, range 62-138. For all tests, except for TMT Delta measuring executive function, higher scores indicate better performance.

Table 3A. Effect of pain (dichotomous) at baseline on major cognitive impairment [a] in older adults [b]

Cognitive domain [c]	**Incident Major Cognitive impairment (N)**	**Pain** [d] **(ref=no pain)**	**Model 1** [e] **HR (95%CI)**	**p value**
Attention N=370	Event=56	Pain (n=243)	.83 (.48-1.46)	.519
Executive function N=382	Event=60	Pain (n=247)	1.02 (.59-1.74)	.949
Memory N=377	Event=49	Pain (n=252)	.99 (.54-1.81)	.962

a. Major cognitive impairment is defined as a score of -1SD below the mean at baseline.

b. Reported as HR with 95% CI derived from Cox regression analysis.

c. Attention: RBANS, range 62-138; Executive function: TMT Delta, range 0-300; Memory: RBANS, range 62-138. For all tests, except for the Trails Tests, higher scores indicate better performance.

d. Pain: 1. No pain (0) (Reference group); 2. Pain severity (1-20).

e. Model 1: Adjusted for age, sex, ethnicity, and education.

Continuous pain measure

Pain severity (measured continuously 1-20; mean = 6.21, SD = 4.10) was associated with major cognitive impairment on memory (HR per one-point increase in pain severity scale = 1.15, 95% CI = 1.06-1.24) after adjustment for age, gender, ethnicity, and education. The association remained significant after additional adjustments for depressive symptoms, GHS, and psychiatric and analgesic medications use. There was no association between pain severity and incident impairment in the attention or executive function domains (Table 4A).

Table 3B. Effect of pain severity (quartiles) at baseline on major cognitive impairment [a] in older adults [b]

Cognitive domain [c]	Incident Major Cognitive impairment (N)	Pain [d] (ref=no pain)	Model [e] HR (95%CI)	p value
Attention N=370	Event=56	No pain (n= 127)	1.0	
		Low pain (n=93)	0.99 (.51-1.90)	.968
		Medium pain (n=76)	0.79 (.31-1.51)	.351
		High pain (n=74)	0.76 (.33-1.76)	.525
Executive function N=382	Event=60	No pain (n=135)	1.0	
		Low pain (n=101)	0.75 (.38-1.51)	.425
		Medium pain (n=77)	1.19 (.60-2.36)	.612
		High pain (n=69)	1.35 (.64-2.84)	.427
Memory N=377	Event=49	No pain (n=125)	1.0	
		Low pain (n=94)	0.62 (.27-1.41)	.253
		Medium pain (n=80)	0.92 (.41-2.09)	.846
		High pain (n=78)	2.03 (.95-4.36)	.069

a. Major cognitive impairment is defined as a score of -1SD below the mean at baseline.
b. Reported as HR with 95% CI derived from Cox regression analysis.
c. Attention: RBANS, range 62-138; Executive function: TMT Delta, range 0-300; Memory: RBANS, range 62-138. For all tests, except for the Trails Tests, higher scores indicate better performance.
d. Pain severity quartiles: 1. No pain (0) (reference group); 2. Low pain (1-4); 2. Medium pain (5-8); 3. High pain (9-20).
e. Model 1: Adjusted for age, sex, ethnicity, and education.

Table 4A. Association between pain severity score [a] at baseline and development of major cognitive impairment [b] in older adults with pain [c]

Cognitive domain [d]	Incident major cognitive impairment (N)	Model 1 [e] HR (95%CI)	p value	Model 2 [f] HR (95%CI)	p value
Attention N=243	Event=35	0.99 (.91-1.08)	.823	1.00 (.91-1.09)	.942
Executive function N=247	Event=38	1.06 (.98-1.14)	.127	1.05 (.97-1.13)	.201
Memory N=252	Event=31	1.15 (1.06-1.24)	.001	1.14 (1.05-1.24)	.002

a. Pain severity is measured continuously (score 1-20).
b. Major cognitive impairment is defined as a score of -1SD below the mean at baseline.
c. Reported as HR with 95% CI derived from Cox regression analysis.
d. Attention: RBANS, range 62-138; Executive function: TMT Delta, range 0-300; Memory: RBANS, range 62-138. For all tests, except for the Trails Tests, higher scores indicate better performance.
e. Model 1: adjusted for age, sex, ethnicity, and education
f. Model 2: adjusted for age, sex, ethnicity, education, GHS, GDS, psychiatric medications, and analgesics.

Pain in tertiles

The distribution-based cut-off points for the pain severity tertiles used in this analysis were justified by the significant associations of the three pain categories with clinically relevant variables in our study sample. Higher levels of pain were associated with higher depression scores on the 30-item Geriatric Depression Scale (GDS)[35] (P for trend = .001), diminished physical activity (P = .009), and more difficulties with activities of daily living (ADLs) (P <.001) (see Supplementary Table).

Supplementary Table. Justification of the pain tertiles

MEAN (SD)	Low pain (1-4)	Medium pain (5-9)	High pain (9-20)	p value *	p value **
GDS score [a] (range 0-30) Mean (SD)	3.97 (3.18)	5.30 (4.61)	5.91 (4.67)	.004	.001
Less physically active (past 12 months) N (%)	28 (26.7%)	33 (37.5%)	40 (44.4%)		.009
ADLs [b] (range 0-14) Mean (SD)	.60 (.99)	1.00 (1.14)	1.23 (1.42)	.001	<.001

* Using ANOVA.

** Linear trend.

a. Geriatric Depression Scale.

b. Activities of daily living (bathing, washing, dressing, walking, feeding, grooming). A higher score indicates more difficulties.

Compared to the 94 participants with low pain at baseline, the 78 participants with a high level of pain had more than a three-fold increased risk of developing major memory impairment (HR adjusted for age, gender, ethnicity, and education = 3.47, 95% CI = 1.42-8.46) (Table 4B). This association persisted after additional adjustment for depressive symptoms, general health, psychiatric medication, and analgesics (HR = 3.09, 95% CI = 1.24-7.68). No significant association was found between pain severity and incident attention or executive function impairment.

Discussion

The results of our study show that there is no difference in the risk of developing major cognitive impairment when older adults with pain of any severity are compared with older adults without pain over an average follow-up of 2.75 years. Pain is a common problem; even in this relatively healthy and ambulatory community-dwelling cohort, 64.6% reported having pain at study baseline. Further analysis revealed that older adults with high levels of pain tend to have a higher risk of developing memory impairment than

their counterparts without pain, and especially compared with those with lower levels of pain. Older adults with high levels of pain have a more than three-fold increased risk of developing major memory impairment than those with low pain. This effect of pain was not found in attention or executive function domains. Even when the effects of potential confounders such as age, gender, ethnicity, education, depressive symptoms, general health, and psychiatric and analgesic medications were taken into account, the independent association between pain severity and memory impairment persisted. Our findings suggest a threshold effect of high levels of pain on cognitive decline in community-dwelling older adults.

Our results are in line with the only other longitudinal study, to our knowledge, reporting that persistent pain was associated with accelerated memory decline and increased probability of developing dementia[13]. Our study adds to these findings and shows that the effects of pain are associated with incident impairment in memory but not in attention and executive function domains. Furthermore, we showed that people with high levels of pain have a significantly higher risk of developing memory impairment than those with low levels of pain. In contrast to cross-sectional clinical studies that revealed deficits in memory, attention, and executive function in chronic pain patients[11,16,40], we did not find an increased longitudinal risk of developing attention or executive function impairment.

Chronic pain in older adults is often undertreated[41,42], especially in those who are cognitively impaired[43,44]. As many as 70% of older adults with chronic pain do not use analgesics on a daily basis, and only 3 to 5% are prescribed opioid analgesics, which might suggest under-treatment[2,42]. In our cohort, only 14% of the older adults with pain reported using analgesics (21% in the highest pain group), including opioids (5.5% in the highest pain group), suggesting that also in our community-residing non-demented sample, pain was substantially undertreated. However, it should be noted that there is a wider variety of treatment options other than medications not captured by our interviews. Physicians are often cautious when prescribing opioids to older adults because of side effects; older adults are even more susceptible developing the side effects of opioids, such as sedation, respiratory depression, constipation, and nausea[45]. Abuse and addiction to opioids are becoming more common as well; however, risk factors for problems with opioid use (overuse, misuse, or abuse) are shown to be a younger age, longer duration, and higher dose of opioids[46].

Moriarty and colleagues have described several mechanisms whereby chronic pain may affect cognition[11]. The limited resources theory explains the pain-cognition relationship on a neuroanatomical level where multiple brain regions are involved in both pain processing and cognitive processes and therefore compete with each other. Brain regions activated

Table 4B. Association between pain severity (tertiles) at baseline and development of major cognitive impairment [a] in older adults with pain[b]

Cognitive domain [c]	Incident major cognitive impairment (N)	Pain Severity Groups [d]
Attention **N=243**	**Event=35**	Low pain (n= 93) Medium pain (n=76) High pain (n=74)
Executive function **N=247**	**Event=38**	Low pain (n= 101) Medium pain (n=77) High pain (n=69)
Memory **N=252**	**Event=31**	Low pain (n= 94) Medium pain (n=80) High pain (n=78)

a. Major cognitive impairment is defined as a score of -1SD below the mean at baseline.

b. Reported as HR with 95% CI derived from Cox regression analysis.

c. Attention: RBANS, range 62-138; Executive function: TMT Delta, range 0-300; Memory: RBANS, range 62-138. For all tests, except for the Trails Tests, higher scores indicate better performance.

in pain processing include the anterior cingulate cortex, insular cortex, thalamus, and prefrontal cortex,[47] and these regions are also involved in cognitive processes. In addition, pain demands attention, and this may take precedence over other cognitive tasks demanding attention[48]. Changes in brain morphology due to neuroplasticity in chronic pain patients can also impair cognitive function. Less total grey matter volume has been found in chronic back pain patients[49]. Pain-induced changes in neuromediators such as gamma-aminobutyric acid (GABA) can also affect cognition[50], and changes in neurotrophic factors (eg, brain-derived neurotrophic factor [also known as BDNF]) may affect neurogenesis[51], important for hippocampal-dependent learning and memory[52]. Although some of the preceding mechanisms may explain the effect of pain on cognition on multiple domains, the neuroplastic changes may explain, in part, the long-term memory impairments in older adults with pain. It is also possible that other underlying mechanisms, such as inflammation, may mediate the association between pain and memory. Previous studies suggested a link between systemic inflammation and weakened pain regulation in chronic pain [53]. Research also implicates biological derangements in inflammation in the occurrence of disorders in gait and cognition in aging, but pain was not included in these analyses[54]. Future studies should explore the neural and biological basis of our findings.

This study has several strengths, including the longitudinal design and the use of standardized valid and reliable pain and cognitive instruments. We used data from a prospective longitudinal study of community-dwelling older adults, which supports the

Model 1 [e] HR (95%CI)	p value	Model 2 [f] HR (95%CI)	p value
1.0		1.0	
0.70 (.31-1.59)	.390	0.66 (.29-1.52)	.334
0.84 (.36-1.97)	.689	0.91 (.37-2.21)	.831
1.0		1.0	
1.64 (.77-3.52)	.201	1.50 (.69-3.26)	.306
1.77 (.78-3.99)	.169	1.61 (.70-3.70)	.259
1.0		1.0	
1.55 (.60-4.03)	.367	1.52 (.57-4.00)	.402
3.47 (1.42-8.46)	.006	3.09 (1.24-7.68)	.015

d. Pain severity tertiles: 1. Low pain (1-4) (reference group); 2. Medium pain (5-8); 3. High pain (9-20).
e. Model 1: Adjusted for age, sex, ethnicity, and education.
f. Model 2: Adjusted for age, sex, ethnicity, education, GHS, GDS, psychiatric medications, and analgesics.

generalizability of our findings to other community populations. We limited potential bias by using appropriate analytical methods, including controlling for a number of potential confounders. Last, in our secondary analyses, we focused only on participants with pain to look at the effect of severity of pain on cognition, allowing us to examine if higher levels of pain lead to a higher risk of developing cognitive impairment, which may support causality between pain and cognition.

An important limitation is that we were not able to quantify the duration of pain. In our study, people were asked to rate their pain over the past month. However, the relatively low back conversion rate of high levels of pain to no pain (13.1%) suggests that pain assessed at baseline in our participants might have been longer than the 4-week period used as the assessment interval in the MOS questionnaire[23]. However, it is still unclear whether the pain between the assessments was persistent or whether the participants had pain-free periods.

The source of pain was also not captured by the questionnaire. The effects of duration and source as well as severity of pain need to be further studied in the context of cognitive decline. Furthermore, to our knowledge, there are no fixed cut-off points for the MOS pain severity scale. Our relatively healthy community-based sample also only had very few individuals who reported extreme pain scores; therefore, we used distribution-based cut-off points.

Another important limitation is that we might have had limited statistical power to detect small changes in cognitive performance over time. A longer follow-up period or a larger sample might have revealed cognitive effects of pain on domains besides memory and significant differences compared with adults without pain, although effect sizes might be expected to be smaller. In addition, our results remained unchanged after accounting for several important confounders, including medication use, which lends confidence to our findings. However, as with any observational study design, the possibility of unmeasured or residual confounding remains.

In contrast with previous cross-sectional studies that are limited in inferring temporality of the relationship between pain and cognition, we showed strong effects of high levels of pain on memory impairment over time. However, future epidemiologic studies with longer follow-up and more comprehensive pain assessments are needed to support causality. Additionally, intervention studies are needed to investigate whether potential deleterious effects of pain on cognition may be prevented by effective pain management and whether alleviating pain leads to improvement of cognitive function in cognitively impaired older adults with pain.

Conclusions

Our findings suggest negative impacts of high levels of pain in older adults on memory, but not on attention or executive function. Older adults with high levels of pain are at a higher risk of developing memory impairment over time than those with low levels of pain. Future research should focus on the specific effects of chronic pain on memory and the underlying neural substrates and mechanisms. Given the detrimental effects of high levels of pain on cognition and the common undertreatment of pain in older adults, it is crucial that health professionals pay more attention to pain assessment and management in the care of older adults.

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CHAPTER 6

The role of C-reactive protein in the pain and cognition relationship

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Introduction

Chronic pain is frequently reported by older adults and is associated with systemic inflammation [1]. Cross-sectional and longitudinal studies show that chronic pain – especially severe pain- is associated with worse cognitive function in older adults [2,3]. A weak association between elevated levels of peripheral C-reactive protein (CRP) and cognitive decline has been shown in the general population [4]. Animal studies suggest that inflammation is one of the mechanisms through which pain influences cognitive impairment [5]. However, whether inflammation similarly mediates the relationship between pain and cognitive functioning in humans is unknown. To address this issue, we performed a cross-sectional study using data from the Health and Retirement Study (HRS) to examine whether the inflammatory biomarker, CRP, mediates the association between severe pain and cognition in older adults.

Methods

We used data from the 2008 wave of HRS; a nationally representative cohort of community-dwelling older adults in the United States [6]. We excluded participants with severe cognitive impairment (Telephone Interview for Cognitive Status score of ≤ 8), adults ≤ 65 years old, or those with CRP values of > 10 μg/ml (acute phase reaction). The local Institutional Review Board approved our study.

Participants were asked if they are often troubled with pain, and, if yes, whether it was mild, moderate, or severe. Because the effect of pain on cognition particularly holds for severe/high levels of pain [3], we compared severe to no pain categories. The Telephone Interview for Cognitive Status score (adapted to be administered in-person and by telephone) was used to measure cognition [7] with a composite score (range 0-35). CRP level was used as the measure of inflammation [8]. Age, sex, education, depression, medical burden, and body mass index (BMI) were included as covariates based on their association with pain and cognition.

We applied path analysis to examine both the direct relationship between pain and cognition and the possible mediation effect of CRP simultaneously. Mediation of the pain-cognition relationship was assumed to be an indirect relationship from pain to cognition through CRP. Unadjusted and adjusted models (for age, gender, education, depression, medical burden, and BMI) were analyzed. The path analysis was performed using AMOS v. 24 computer program (IBM SPSS, Chicago, IL).

Results

The mean age of the 2789 included participants was 74.5 years (standard deviation = 6.9) with 1205 men (43.2%) and 1584 women (56.8%) (Table 1). Two hundred twelve participants (7.6%) reported severe pain.

Table 1. Demographic characteristics according to no pain and severe pain in older adults aged 65 years and older (N= 2789)

Characteristic **Mean (SD) or %**	**No pain** **N=2577 (92.4%)**	**Severe pain** **N=212 (7.6%)**	**p value**
Age (years) *Range 65-97*	74.60 (6.92)	73.79 (6.43)	.099
Gender Women	1419 (55.1%)	165 (77.8%)	≤.001
Education (years)	12.50 (3.07)	11.03 (3.54)	≤.001
Comorbid conditions [a] *Range 0-8*	2.12 (1.32)	3.25 (1.47)	≤.001
Depression [b]	208 (8.1%)	80 (37.7%)	≤.001
BMI (kg/m^2)	27.15 (5.07)	29.93 (7.00)	≤.001
Total cognition score [c] *Range 0-35*	21.92 (4.64)	20.56 (4.59)	≤.001
CRP (ug/ml) *Range .01-9.95*	1.60 (1.74)	2.17 (2.11)	≤.001

SD, standard deviation.

[a] The presence (1) or absence (0) of one of the following eight physician-diagnosed diseases: hypertension, diabetes, stroke, cancer, arthritis, psychiatric problems, chronic lung disease, and cardiac disease.

[b] Score of ≥ 4 on the 8-item Center for Epidemiologic Studies Depression Scale.

[c] The total composite cognition score Scores ranged from 0 to 35, with higher scores reflecting better performance and sums immediate and delayed recall tests (memory), serial 7s subtraction (working memory), counting backwards (attention and processing speed), object naming (language), recall of the date (orientation), and naming of the current president and vice-president (orientation).

In the unadjusted model, severe pain is associated with worse cognition scores (β = -.08, p < .001). When CRP is included as a mediator in the unadjusted model, the magnitude of the association between severe pain and cognition remains the same (β = -.08, p < .001), indicating that CRP does not mediate this relationship. In this unadjusted model, severe pain was associated with higher CRP levels (β = .09, p < .001), but CRP was not significantly associated with cognition (β = -.03, p =.164).

After adjusting for sex, age, years of education, medical burden, BMI, and depression, the association between severe pain and cognition was no longer significant (β = -.02, p = .32), and this was unchanged when including CRP.

Discussion

In a nationally representative US cohort of older adults, we could not establish a mediating role of CPR in the association between severe pain and cognition because this association was no longer significant after adjusting for multiple confounders.

To our knowledge, this is the first study to examine the association between pain, CRP, and cognition. In contrast to previous findings [2,9], we did not find a significant cross-sectional association between severe pain and cognition or CRP and cognition after adjusting for multiple covariates [1,4]. This might be due to overadjustment in our multivariate models or because the assessment of pain was not optimal and did not include duration and type of pain. Alternatively, pain may only affect cognition over time [10] and the possible effects of inflammation (caused by pain) on cognition need time to develop.

Our study has several strengths, including the large sample and hypothesis-based approach. A limitation of the study was that we examined just 1 inflammatory biomarker. A more comprehensive biomarker panel was not available in HRS.

Future research studies need to clarify the role of inflammation on the longitudinal temporal relationships between pain and cognition.

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CHAPTER 7

THE ASSOCIATION BETWEEN PAIN AND PREVALENT AND INCIDENT MOTORIC COGNITIVE RISK SYNDROME IN OLDER ADULTS

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Abstract

Background: The Motoric Cognitive Risk Syndrome (MCR) is a pre-dementia syndrome characterized by subjective cognitive complaints and slow gait in the absence of dementia and mobility disability. Worse cognitive and motoric function is associated with chronic pain in older adults. Our aim was to study the association between pain and prevalent and incident MCR in adults aged 65 years and older.

Methods: We analyzed the cross-sectional association between severity of pain and prevalent MCR in 3244 older adults participating in the Health and Retirement Study (2008 wave) using logistic regression analysis adjusting for demographic, peripheral, central or biological risk factors. Additionally, we analyzed the longitudinal association between severity of pain and incident MCR in 362 participants in the Central Control of Mobility in Aging Study, using Cox regression analysis.

Results: The 155 Health and Retirement Study participants with severe pain had an increased risk of prevalent MCR (n=249), compared to 2245 individuals without pain (adjusted for demographics OR: 2.78, 95% CI:1.74-4.45).

Over a mean follow-up of 3.01 years (SD 1.38), 29 individuals in the Central Control of Mobility in Aging Study developed incident MCR. Older adults with severe pain had over a five times increased risk of developing incident MCR, compared to those without pain even after adjusting for demographic variables (HR: 5.44, 95% CI: 1.81-16.40).

Conclusion: Older adults with severe pain have a higher prevalence and incidence of MCR. These findings should be further explored to establish if pain is a potentially modifiable risk factor to prevent cognitive decline.

Introduction

The Motoric Cognitive Risk syndrome (MCR) is a pre-dementia syndrome that is characterized by the presence of slow gait and subjective cognitive complaints [1,2]. A multi-country epidemiological study of adults aged 60 years and older showed a prevalence of MCR of 9.7% [2]. The incidence of MCR in four US-based cohorts was 65.2/1000 person years [3]. MCR is a reliable predictor of both Alzheimer's disease (2-fold increased risk) and vascular dementia (over 12-fold risk) [1,2] and it has a better predictive validity for dementia compared to subjective cognitive complaints or slow gait separately [1,2]. The clinical utility of MCR as a predictor is remarkable, since there is no specialized equipment or trained personnel needed to diagnose patients with MCR.

Pain is a frequently reported problem in older adults and is associated with slow gait [4] and cognitive impairment [5-7]. While both of these symptoms are key components of the MCR definition, it is yet unknown whether chronic pain also predicts MCR. Although it is still unknown whether adequate treatment of pain leads to improved cognition, understanding this relationship is important because pain might be a modifiable risk factor for cognitive decline. To address this knowledge gap, we performed two related studies in two independent cohorts to examine whether pain is associated with and predicts MCR. Since pain is associated with slow gait and cognitive impairment, we hypothesized that pain is also a predictor for MCR in older adults. We first analyzed the cross-sectional association between pain and prevalent MCR in the Health and Retirement Study (HRS). Second, we examined the longitudinal association between pain and incident MCR in the Central Control of Mobility in Aging study (CCMA).

Methods

Two independent datasets were used to perform our analyses; The Health and Retirement study (HRS) and the Central Control of Mobility in Aging (CCMA) study. The Einstein institutional review board approved the analysis.

HRS

Data were used from the 2008 wave of the HRS, a cohort of community-dwelling adults, aged 50 years and older. Details of HRS study design are available online at *http://hrsonline.isr.umich.edu*, and have been published [8-10]. The HRS is sponsored by the National Institute on Aging (U01AG009740) and conducted by the University of Michigan. For our analyses, participants with severe cognitive impairment were excluded to minimize underreporting of pain severity. Cognition was assessed using the Telephone

Interview for Cognitive Status (TICS; range 0-35), adapted to be administered in-person [8]. A previously established cutoff score of 8 or less on the TICS was used to exclude participants with major cognitive impairment [11]. We used only the data of participants age 65 and older, because they completed the timed walk test (used to determine MCR) as part of the physical performance measures in HRS.

CCMA

The CCMA study is a prospective cohort study of community-dwelling older adults aged 65 years and older, who reside in lower Westchester County (NY). Detailed descriptions of the study, including eligibility criteria, have been previously published [12]. For our longitudinal analysis, participants with prevalent MCR or dementia were excluded. Also participants who developed incident dementia – without a previous diagnosis of MCR - were excluded. Dementia diagnoses were assigned at consensus case conferences according to the current American Psychiatric Association definition [13]. MCR was defined based on established criteria (described below).

Measures

Pain severity (independent variable)

In HRS, pain is measured in four categories; 1. No pain, 2. Mild pain, 3. Moderate pain, and 4. Severe pain. These categories are based on two questions; "Are you often troubled with pain?" and, if the participants answered this question affirmatively the follow-up question was asked; "How bad is the pain most of the time: mild, moderate, or severe?"

In CCMA, pain was assessed by the 7-item pain questionnaire from the Medical Outcome Study (MOS) [14,15]. Participants were asked to rate their pain on average over the previous 4 weeks, with responses ranging from 0 ('no pain') to 20 ('pain as bad as you can imagine'). We examined the pain score continuously as well as in quartiles to aid clinical applicability to the findings (1. 'no pain': score 0; 2. 'low pain': score 1-4; 3. 'medium pain': score 5-8; 4. 'high pain': score 9-20, where we will refer to as no pain, mild pain, moderate pain, and severe pain, respectively).

MCR syndrome (Outcome)

In both HRS and CCMA, MCR syndrome was defined as the presence of subjective cognitive complaints and slow gait in older adults without mobility disability or dementia [1]. Slow gait has been defined as ≥ 1 standard deviation (SD) below age and sex-specific means, which has been applied before in HRS [4,16] and CCMA [2] to define MCR. In HRS, gait speeds (in meter/second) were calculated from time in seconds recorded as participants

walked at normal pace over a 2.5-meter course in their homes. In CCMA, research assistants measured gait speed (meters/second) at normal pace using an 8.5 meter long computerized walkway (GAITRite; CIR Systems, PA), which has excellent reliability [17,18]. To account for differences in gait measurements between cohorts, a universal slow gait cut-score was not applied; but study population specific cut-scores were used; consistent with previous MCR publications in these and other cohorts [2,3,19,20].

In HRS, the presence of subjective cognitive complaints was based on two questions: 1.*"How would you rate your memory at the present time? Would you say it is excellent, very good, good, fair or poor?"* and 2.*"Compared with the previous interview, would you say your memory is better now, about the same, or worse now than it was then?".* 'Fair' and 'poor' responses to the first question, or 'worse' to the second question, were coded as positive. In CCMA, subjective cognitive complaints were based on a 'yes' response to the memory item on the Geriatric Depression Scale [21] or a score of ≥1 on the AD8 dementia screener [22].

Covariates

In HRS, we selected several sociodemographic (age, gender, race/ethnicity, and years of education) and health variables to include as possible confounders based on reported associations with pain or cognition. Physical inactivity was defined as participating in vigorous sports or activities (including cycling, running or jogging, aerobics or gym workout, tennis, or digging) less than once a week [4,8]. Obesity was defined as a body mass index (BMI) of ≥ 30 kg/m^2 [8]. Poor distance vision was defined as self-rated "poor" ability to see objects at far distances. The occurrence of falls (yes/no) over the previous 2 years was recorded. Vascular disease (yes/no) was defined by the presence of any of the following disorders: hypertension, heart disease, diabetes or stroke. Depressive symptoms were measured using the 8-item Center for Epidemiologic Studies Depression Scale, and a score of ≥ 4 was considered elevated [23,24]. Tobacco use (yes/no), was based on the following question: "Do you smoke cigarettes now?". Cognition was assessed using the Telephone Interview for Cognitive Status (TICS; range 0-35), adapted to be administered in-person [8]. C-reactive protein was included as a marker of inflammation [25]. CRP was collected at the University of Vermont through an enzyme-linked immunosorbent assay using dried blood spot and measured in µg/mL [26]. CRP values above 10 µg/mL suggest a possibility of an acute phase response [27], and were therefore excluded. Special informed consent was acquired, and completion rate was 87%.

In CCMA, age, gender, race and years of education were assessed by the research assistants at the baseline interview. Since the size of the CCMA study sample was fairly small, with only 29 incident cases of MCR, we limited the number of covariates to those strongly correlated with cognition and gait. General mental status was assessed with the

total score on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), an omnibus test of various cognitive domains. Gait speed and cognition were measured as described before.

Statistical analysis

In HRS, we analyzed demographic and health characteristics according to the pain quartiles (no pain, mild, moderate and severe pain). Between group differences were analyzed using chi-square tests or Fisher's exact test for categorical measures and analysis of variance (ANOVA) for continuous measures. Next, we analyzed the association between pain and prevalent MCR (yes/no) using logistic regression analysis. We created five multivariate models, adjusting for mechanisms that might influence this association. In these models we are subsequently adjusting for: 1. Demographic factors (age, gender, race, education); 2. 'Peripheral' factors, i.e those factors that are more likely to affect cognitive or motor function via peripheral effectors organs, (physical inactivity, obesity, poor distance vision, falls), though some of these risk factors also may have central effects; 3. 'Central' risk factors i.e. the factors that are more likely to affect cognitive or motor function via central pathways of cognitive processing (age, vascular disease [=heart disease, hypertension, diabetes or stroke], depression, tobacco use, education [as a measure of cognitive reserve] and cognition); 4. Biological factor (inflammation measured by CRP levels). Model 5 is the overall model, adjusted for all the covariates at once.

In the CCMA cohort, we reported demographic and health characteristics for the study population as well as separately for participants who developed MCR during follow-up (incident MCR) and those who did not (no incident MCR). Similar statistical methods were used as described above to examine baseline characteristics. Next, we analyzed the association between pain severity at baseline and incident MCR over follow-up using Cox regression analyses, adjusted for age, gender, race, and education (Model 1). In Model 2, we additionally adjusted for cognition (RBANS total score) and gait speed at baseline to account for pre-existing gait abnormalities and cognitive status. Given the relatively small sample size and lower number of incident MCR cases, we limited the number of covariates in our analyses to those that were the most relevant. Pain severity was analyzed continuously (0-20) as well as in categories (1. No pain [reference group]; 2. Mild pain; 3. Moderate pain; and 4. Severe pain). Hazard ratios (HRs) with 95% Confidence Intervals (CI) were reported. The follow-up time was reported in years. Proportional hazard assumptions of the models were examined analytically and graphically.

All analyses were performed using SPSS v. 24 (SPSS Inc., Chicago, IL).

Results

In the 3244 HRS participants the mean age was 74.31 (SD= 6.77), and 59.0% were female; for the 362 CCMA participants the mean age was 76.47 (SD = 6.31) and 56.9% were female. The prevalence of MCR was 7.7 % (n=249) in HRS and 29 (8.0%) of the 362 participants included in the longitudinal analysis in the CCMA study developed incident MCR during follow-up.

HRS – prevalent MCR

The complete HRS includes 37,319 participants; this study only uses data from the 2008 wave. Excluding participants in the 2008 wave without CRP, reduced the eligible sample to 6181 participants, and to 5944 after exclusion of CRP > 10 µg/mL. Furthermore, participants aged <65years were excluded, which reduced the sample to 3916 participants. Participants who were missing variables for MCR diagnosis (n=569) or pain (n=5), as well as those with severe cognitive impairment (n=31), or who were missing values on any of the covariates (n=67) were excluded. Of the 3244 HRS participants in the final study sample, 2245 experienced no pain, 307 mild pain, 537 moderate pain and 155 severe pain (Table 1).

The prevalence of MCR increased with increasing pain severity; 6.0% in participants without pain, 9.1% in participants with mild pain, 10.8% in those with moderate pain and 18.7% in those with severe pain (p-value ≤.001). Participants with higher pain severity were more likely to be female, not White, to have fewer years of education, to be physically inactive, to be obese, to have poor vision for distances, to have experienced falls in the past two years, to have a vascular disease, depression, lower cognitive score, and higher CRP level.

Table 2 shows that pain severity is associated with MCR cross-sectionally. After adjusting for demographic variables, older adults with severe pain are almost three times more likely to have a diagnosis of MCR (Model 1. OR: 2.78, 95% CI: 1.74-4.45), compared to those without pain. Even after adjusting for peripheral, central, or biological risk factors (Models 2-4), participants with moderate and severe pain have a higher risk of MCR, compared to those without pain. After adjusting for all the different risk factors (Model 5), older adults with moderate pain only had a borderline increased risk of MCR, compared to those without pain (OR: 1.43, 95% CI: 1.00-2.04, p-value .051), though the association with severe pain remained in the same direction (OR 1.59, 95% CI .96-2.65).

Table 1. Demographic characteristics according to pain severity in older adults aged 65 years and older at baseline in HRS, N=3244

Characteristic Mean (SD) or N (%)	PAIN SEVERITY AT BASELINE				
	No pain N=2245	**Mild pain N=307**	**Moderate pain N=537**	**Severe pain N=155**	**p value***
Age (in years)	74.40 (6.79)	73.48 (6.94)	74.47 (6.59)	74.09 (6.62)	.140
Gender					≤.001
Women	1261 (56.3%)	169 (55.0%)	359 (66.9%)	121 (78.1%)	
Men	981 (43.7%)	138 (45.0)	178 (33.1%)	34 (21.9%)	
Ethnicity					.013
White	1919 (85.5%)	269 (87.6%)	480 (89.4%)	127 (81.9%)	
Black	263 (11.7%)	30 (9.8%)	39 (7.3%)	18 (11.6%)	
Other	63 (2.8%)	8 (2.6%)	18 (3.4%)	10 (6.5%)	
Years of education	12.57 (3.04)	12.44 (3.09)	12.26 (2.92)	10.91 (3.52)	≤.001
Physical inactivity [a]	1488 (66.3%)	204 (66.4%)	427 (79.5%)	121 (78.1%)	≤.001
Obesity [b]	563 (25.1%)	101 (32.9%)	199 (37.1%)	74 (47.7%)	≤.001
Poor Vision [c]	53 (2.4%)	14 (4.6%)	27 (5.0%)	18 (11.6%)	≤.001
Falls [d]	692 (30.8%)	147 (47.9%)	263 (49.0%)	91 (58.7%)	≤.001
Vascular Disease [e]	1675 (74.6%)	252 (82.1%)	457 (85.1%)	142 (91.6%)	≤.001
Depression	160 (7.1%)	40 (13.0%)	97 (18.1%)	52 (33.5%)	≤.001
Tobacco use (now)	213 (9.5%)	21 (6.8%)	45 (8.4%)	14 (9.0%)	.450
Cognition [f]	22.22 (4.51)	22.21 (4.39)	22.04 (4.54)	20.89 (4.52)	.005
MCR	134 (6.0%)	28 (9.1%)	58 (10.8%)	29 (18.7%)	≤.001
CRP [g]	1.58 (1.72)	1.61 (1.61)	1.78 (1.89)	2.02 (1.96)	.003

* Using ANOVA for continuous variables and chi-square test or Fisher's exact test for categorical variables.

e. Vigorous active less than once a week.

f. BMI ≥30 kg/m^2.

g. Self-rated poor distant vision.

h. Falls in the past two years.

i. Vascular disease: Heart disease, hypertension, diabetes or stroke.

j. Total TICS score, range 0-35.

k. CRP in µg/mL.

Table 2. Association between pain and MCR in HRS among older adults, using logistic regression

	NO PAIN (REF)	MILD PAIN	MODERATE PAIN	SEVERE PAIN
Model 1 [a]	1	1.64 (1.05-2.56)*	1.98 (1.42-2.78)**	2.78 (1.74-4.45)**
Model 2 [b]	1	1.32 (.86-2.05)	1.42 (1.02-1.99)*	2.30 (1.44-3.66)**
Model 3 [c]	1	1.43 (.92-2.24)	1.61 (1.14-2.27)*	1.99 (1.23-3.24)*
Model 4 [d]	1	1.59 (1.03-2.43)*	1.85 (1.34-2.56)**	3.42 (2.19-5.32)**
Model 5 [e]	**1**	**1.30 (.82-2.06)**	**1.43 (1.00-2.04)**	**1.59 (.96-2.65)**

Note: Results reported as odds ratios (OR) with 95% CI.

a. Model 1: adjusted for demographic characteristics (age, gender, race, education).

b. Model 2: adjusted for peripheral risk factors (physical inactivity, obesity, poor distant vision, falls).

c. Model 3: adjusted for central risk factors (age, cardiovascular disease (=heart disease, hypertension, diabetes or stroke), depression, tobacco use, education and cognition (TICS)).

d. Model 4: adjusted for biological factors (inflammation).

e. Model 5: adjusted for all factors above (model 1-4).

** p value ≤.05*

*** p value ≤.001*

CCMA – incident MCR

At baseline, 588 participants were included. After excluding participants with no follow-up data (including those who have not yet had their 1-year follow-up at the time of data analysis) (n=154), prevalent MCR (n= 41), prevalent dementia (n=12), adults that developed dementia before their MCR diagnosis (n=15), or participants with missing values on covariates (n=4), 362 older adults (mean age 76.47 years (SD = 6.31), 56.9% female) were eligible for the longitudinal analysis. The mean follow-up was 3.01 years (SD 1.38), range 0.85 to 7.04 years. Table 3 shows that participants who developed MCR during follow-up were more likely to be older, have a slower gait speed at baseline and have more severe pain at baseline.

Pain severity, measured continuously (0-20), was associated with an increased risk of developing incident MCR, after adjusting for age, sex, race, and education (HR: 1.13, 95% CI 1.05-1.22) (Table 4). Older adults with severe pain had a more than five times increased risk of developing MCR, compared to those without pain (HR: 5.44, 95% CI: 1.81-16.40). Additional adjustment for cognitive scores (RBANS) and gait speed at baseline, did not alter the results (Table 4 and Model 2). We have performed additional adjustments for a general health score (summing the presence of diabetes, chronic heart failure, arthritis, hypertension, major depression, stroke, Parkinson disease, chronic obstructive lung disease, angina, and myocardial infarction; range 0-10), BMI (kg/m^2), physical activity (less physical active in the past 12 months), history of tobacco use and falls (any falls in the last 12 months). Since these additions did not alter our results, we did not include these results in our final multivariable

model (data not shown). Figure 1 shows the results of the Cox regression analysis displaying the time to MCR on the X-axis and the probability of MCR on the Y-axis. Older adults with severe pain have a higher hazard curve compared to those without pain, since they are more likely to develop MCR.

Table 3. Demographic characteristics according to incident MCR [a] in 362 older adults in the CCMA cohort.

Characteristic **Mean (SD) or N (%)**	**OVERALL** **N=362**	**No incident MCR** **N=333**	**Incident MCR** **N=29**	**P-value***
Age (in years)	76.47 (6.31)	76.13 (6.11)	80.36 (7.32)	≤.001
Gender				.497
Women	206 (56.9%)	190 (57.1%)	16 (55.2%)	
Men	156 (43.1%)	143 (42.9%)	13 (44.8%)	
Race				
Caucasian	295 (81.5%)	273 (82.0%)	22 (75.9%)	.274
Black	55 (15.2%)	48 (14.4%)	7 (24.1%)	
Other	12 (3.3%)	12 (3.6%)	0 (0%)	
Years of education	14.75 (2.90)	14.76 (2.90)	14.59 (2.87)	.757
RBANS (cognition)	93.73 (11.36)	93.90 (11.50)	91.72 (9.54)	.322
Gait speed (cm/s)	101.95 (22.07)	103.64 (21.35)	82.63 (21.33)	≤.001
Pain (range 0-20)	4.11 (4.54)	3.87 (4.41)	6.86 (5.21)	.001
Pain				.017
No pain	128 (35.4%)	122 (36.6%)	6 (20.7%)	
Mild pain	92 (25.4%)	86 (25.8%)	6 (20.7%)	
Moderate pain	72 (19.9%)	67 (20.1%)	5 (17.2%)	
Severe pain	70 (19.3%)	58 (17.4%)	12 (41.4%)	

* Using t-test analysis for continuous variables and chi-square test or Fisher's exact test for categorical variables.

Table 4. Effect of pain severity at baseline on MCR in 362 older adults in the CCMA cohort[a]

INCIDENT MCR (N)	PAIN	MODEL 1 [B] HR (95%CI)	P-VALUE	MODEL 2 [C] HR (95%CI)	P-VALUE
Event= 29	Continuously (0-20)	1.13 (1.05-1.22)	.001	1.12 (1.04-1.21)	.002
	Categories [d]				
	No pain (n= 128)	1.0		1.0	
	Mild pain (n=92)	1.91 (.59-6.16)	.281	2.86 (.86-9.49)	.086
	Moderate pain (n=72)	1.97 (.59-6.59)	.273	1.99 (.57-6.91)	.279
	Severe pain (n=70)	5.44 (1.81-16.40)	.003	5.66 (1.83-17.52)	.003

a. Reported as hazard ratio with 95% CI derived from Cox regression analysis.

b. Model adjusted for age, sex, race, and education.

c. Model adjusted for age, sex, race, education, cognition (RBANS), and gait speed.

d. Pain severity quartiles: 1. No pain (0) (reference group); 2. Mild pain (1-4); 2. Moderate pain (5-8); 3. Severe pain (9-20).

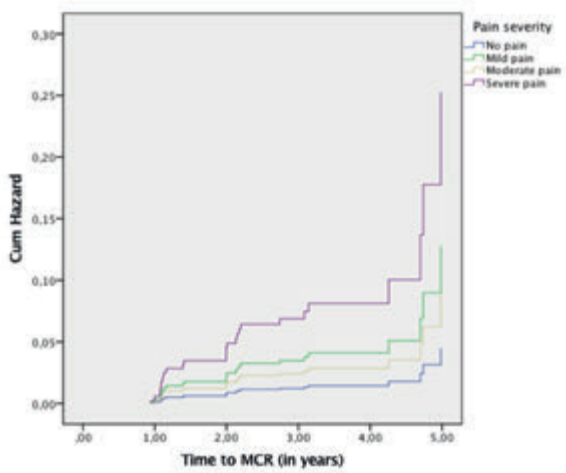

Figure 1. Effect of pain severity [a] at baseline on MCR in 362 older adults in the CCMA cohort [b]

[a.] Pain severity quartiles: 1. No pain (0) (reference group); 2. Mild pain (1-4); 2. Moderate pain (5-8); 3. Severe pain (9-20).

[b.] Model adjusted for age, sex, race, education, cognition (RBANS), and gait speed.

Discussion

Our study in two independent cohorts showed that pain is associated with both prevalent and incident MCR in community-dwelling older adults. In a U.S. nationally representative cohort of older adults, those with severe pain had an increased risk of prevalent MCR, compared to those without pain, after adjusting for demographic, peripheral, central, or biological risk factors. When we adjusted the association between pain and prevalent MCR for all possible confounders together, the association between severe pain and MCR was not significant though in the same direction. It is possible that adjusting for all these factors results in overadjustment, which causes the association between severe pain and MCR to disappear. The reduction in effect size suggests that the effect of pain on MCR may be via some of these confounders. A second independent cohort showed that older adults with severe pain had a more than five times increased risk of developing incident MCR, compared to those without pain.

To our knowledge, this is the first study examining the association between pain and MCR. Previous cross-sectional studies have shown an association between pain and worse cognition in older adults [5,7]. In HRS, a longitudinal analysis showed that persistent moderate to severe pain at baseline is associated with accelerated memory decline and increased risk of dementia in older adults [28]. In CCMA, older adults with high levels of pain have an over three-fold increased risk of developing major memory impairment compared to those with low levels of pain [6].

Pain might be associated with MCR, because overlapping brain regions are involved in pain processing, cognitive processes and gait, and therefore these three might interact with each other. For instance insular and prefrontal cortex regions are activated in both pain processing [29] and MCR [20]. It is also possible that underlying biological processes mediate the relationship between pain and MCR, including inflammation. C-reactive protein levels predict mobility disability and accelerated gait speed decline in older adults [30]. Also, chronic pain is associated with inflammation and increased levels of inflammatory markers [31-33], and systemic inflammation is associated with cognitive decline and Alzheimer's Disease [34,35]. We account for inflammation in our analyses.

Our findings might be important for clinical practice, given the high prevalence of chronic pain among older adults: more than half of the older adults living in the community and up to 70% of older adults in residential homes, experience pain [36,37]. However, chronic pain is often undertreated in older adults [38], especially in those who are cognitively impaired [39,40].

This study has several strengths, including the use of two independent cohorts to examine prevalence and incidence of MCR. We did not use HRS to examine the incident MCR outcome as physical assessments were repeated only at four-year intervals. The longitudinal analysis in the CCMA cohort supports a temporal sequence of pain preceding the onset of MCR. Limitations include the use of self-report pain measures. The duration of pain is not assessed in HRS, so we are not able to distinguish acute from chronic pain. Excluding participants who have experienced transient acute pain, might even strengthen the association between pain and prevalent MCR. The prevalence of pain in HRS was 30.8%, which was relatively low compared to results showing that more than half of community-dwelling older adults experiences chronic pain [36]. Two different pain scales were used in CCMA and HRS. Therefore, we do not assume that all categories correspond. This might result in detection bias, where an overestimation of severe pain could lead to an underestimation of the association between pain and MCR. When adjusting the association between pain and prevalent MCR for all possible confounders together, the association between severe pain and MCR was not significant though in the positive direction. We did not include pain medications as there were many missing values (n=329). Lastly, the longitudinal CCMA sample was relatively small, limiting the number of covariates.

Our findings suggest that severe pain in older adults is associated with an increased risk of prevalent and incident MCR. Given the detrimental effects of pain and the high prevalence of undertreatment of pain in older adults, our observations may point to a possible prevention strategy of cognitive decline, namely an adequate treatment of (chronic) pain, especially for individuals who develop dementia via the MCR pathway. Future research should focus on the question whether treatment of pain leads to reduced cognitive decline or even to improved cognitive functioning.

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Chapter 8

General discussion

General discussion

The aim of our studies was to enhance the understanding of how chronic pain is associated with several domains of cognitive functioning. First, we examined the cross-sectional association between chronic pain and various cognitive domains (attention, executive functioning, memory, and general cognitive performance) in older adults. Then, we investigated whether a tool to measure different domains of attention, is also useful for measuring attention in the very old. Subsequently, we focused on the association between pain and specific domains of attention (selective, sustained, and divided attention and attentional switching). We also determined the association between pain and cognition over time. Next, we explored a mechanism how pain may affect cognition by investigating the possible mediating role of inflammation in the pain-cognition relationship. Finally, we examined the association between pain and prevalent and incident motoric cognitive risk syndrome (MCR); a pre-dementia syndrome. We used data from three independent datasets in this thesis, the Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly (MOBILIZE) Boston Study, the Central Control of Mobility in Aging study (CCMA) Study, and the Health and Retirement Study.

In this chapter, the main findings from *chapter 2* to *chapter 7* will be reviewed and discussed in the context of current scientific literature. Also methodological considerations, potential implications for clinical practice and ideas for future research will be discussed.

1. *MOBILIZE Boston study*
   The Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly (MOBILIZE) Boston Study is a population-based study of 765 participants aged 70 and older. Pain severity and interference scales were measured and a large panel of cognitive tests. In the sixth-year follow-up assessment, referred to as MOBILIZE II, various domains of attention were measured.
2. *Central Control of Mobility in Aging study*
   The Central Control of Mobility in Aging study (CCMA), including 590 non-demented community-residing individuals, aged 65 and older, enrolled between June 2011 and September 2017. A pain severity scale is included and a large battery of cognitive tests. Also, presence or absence of a MCR diagnosis is included.
3. *The Health and Retirement Study*
   The ongoing Health and Retirement Study (HRS) is a nationally representative longitudinal survey of more than 37 000 individuals older than 50 years old in the US. The sample was built up over time and merged with additional cohorts to become a national representative cohort of U.S. community-dwelling adults aged 51 years and older in 1998. Pain severity, cognitive measures, and C-reactive protein (CRP) levels were included.

Summary of the main findings

In *chapter 2* we studied the association between pain severity and interference with cognitive functioning cross-sectionally using data of the MOBILIZE Boston Study. Our main conclusion is that although, as previous studies already showed, there certainly is an association between (chronic) pain and cognitive functioning, the nature of that association is complex. Pain interference (with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life), but not pain severity, was associated with impaired memory and general cognitive performance in older adults after adjusting for demographics, chronic conditions, behaviors including alcohol use and physical activity, and psychiatric medications. The associations between pain severity and interference and other domains of cognitive functioning were not statistically significant anymore after adjusting for all these confounders.

The aim of the study reported in *chapter 3* was to analyze whether the Test of Everyday Attention (TEA) would be a valuable test to measure multiple domains of attention in community-living adults of 80 years and older, participating in the six-year follow-up assessment of the MOBILIZE Boston Study (MOBILIZE II). We showed that the TEA might be a valuable test to measure multiple domains of attention in these very old, although one subtest of the TEA, measuring attentional switching, was probably challenging, resulting in a relatively high number of incomplete tests.

In *chapter 4*, we analyzed whether chronic pain is associated with attentional challenges, measured with the TEA, in community-living older adults in MOBILIZE II. Higher pain severity was associated with poorer scores in measures of selective and sustained attention. Pain interference scores were also significantly inversely associated with selective attention.

Next, in *chapter 5*, we aimed to analyze the longitudinal relationship between pain and cognition using the data of the CCMA study. We found that in older adults, the presence of severe pain at baseline increases the risk of developing incident memory impairment. However, pain does not increase the risk of developing attention or executive functioning impairment.

Our aim of the study reported in *chapter 6* was to clarify a possible mediating role of C-reactive protein (CRP) in the relationship between pain and cognition using data from the Health and Retirement Study. However, we could not establish a mediating role of CRP in the association between severe pain and cognition, because in our dataset this association was no longer significant after adjusting for multiple confounders.

The final aim of our research described in *chapter 7*, was to describe the cross-sectional and longitudinal association between pain and MCR in the HRS and the CCMA Study, respectively. We found that older adults with severe pain had a higher prevalence and incidence of MCR. In HRS, those with severe pain had an increased risk of prevalent MCR, compared to those without pain, after adjusting for demographic, peripheral, central or biological risk factors. After adjusting for all the risk factors together, the association between severe pain and MCR was not significant anymore, although in the same positive direction. In the CCMA Study, older adults with severe pain had a more than five times increased risk of developing incident MCR, compared to those without pain, over a mean follow-up of 3.01 years (SD 1.38).

Findings in the context of current scientific literature

Chronic pain and cognition cross-sectionally

Previous reviews on pain and cognition showed cross-sectional associations between chronic pain and decreased functioning on several domains of cognitive functioning, including attention, psychomotor speed and processing speed, executive functioning and memory [1,2]. Our results are partly in line with the results found in earlier studies: we found associations between higher pain severity and impaired memory, executive functioning and general cognitive performance, and between higher pain interference and impaired attention, memory, executive functioning and general cognitive performance after adjustments for age, gender, race, and education. However, in our study many of these associations were not statistically significant anymore after additional adjustments for chronic conditions and psychiatric medications. Although, the association between pain interference and impaired memory and general cognitive performance persisted. Pain and depression often co-occur [3] and our results showed that additional adjustments for medications and chronic conditions, including depression, in the analyses had a substantial impact on the pain – cognition relationship, suggesting that depression might be involved in the causal pathway between pain and cognitive function [4]. Previous studies reporting associations between chronic pain and cognition often did not adjust for all possible confounders that we, based on previous literature [5,6], have included in our analyses and this might explain the differences between our findings and the results of the aforementioned reviews. It is possible that not pain, but comorbidity or factors associated with pain, such as depression [7] and analgesics [8], are the risk factors for cognitive impairment. Lee and colleagues also showed that the association between chronic widespread pain and processing speed was partially mediated by depressive symptom severity [9]. Karp and colleagues showed an association between pain severity and executive functioning, which was only borderline significant after adjusting for the effects of depression, sleep, medical comorbidity, opioid use and years of education (p=.056) [10]. A recent review on the relationship between chronic

pain and neurocognitive function showed that several factors might moderate this relationship, including mood symptoms, medication side effects and intensity and/or chronicity of pain [11]. Additional adjustments for chronic conditions and psychiatric medications also attenuated our results. But our results did not change after including opioids in the multivariate analyses. However, it should be noted that only a low number of participants was using opioids. Previous studies showed mixed results regarding the possible mediating role of opioids in the relationship between chronic pain and cognitive functioning; some suggest improvement in cognitive functioning probably because of pain control, while others results suggest that memory and attention are probably impaired because of medication side effects [11].

Pain and attention

Our results that chronic pain is associated with specific domains of attention in community-living older adults are in line with several studies showing disruptions in selective and sustained attention and in working memory (which is often categorized as a more complex form of attention) in chronic pain patients [8,12-14]. This is also consistent with our previous findings that pain demands attention and takes precedence over other attention-demanding cognitive tasks; we also found that the observed relationships between pain and cognitive performance were partly explained by the effect of pain on attentional resources in the MOBILIZE Boston Study, consistent with Eccleston's cognitive affective theory [15]. Similarly, a study of chronic pain patients also showed that the association between chronic pain and memory performance was partially explained by attentional dysfunction [5]. In other words, pain can be distracting and this is might affect test results when participants are also experiencing chronic pain during neuropsychological testing. Nearly all participants in the MOBILIZE study with chronic pain reported they were experiencing pain on the day of the cognitive testing.

Chronic pain and cognition longitudinally

The mixed picture of the cross-sectional associations between pain and cognition we and other researchers found, raised the question about the longitudinal relationship between pain and cognition. We found that severe pain is associated with incident memory impairment, but not with incident attention or executive function impairment. There are only two previous studies analyzing the longitudinal associations between pain and cognition. Similar to our findings that severe pain is associated with incident memory impairment, Whitlock and colleagues reported that persistent pain was associated with accelerated memory decline and increased probability of developing dementia [7]. It is unclear whether other domains of cognitive functioning were not studied or that they were not reported since no significant associations were found. In contrast, a study using data from an English nationally representative longitudinal study

reported that pain is not associated with cognitive decline in older adults. However, similar to our results, they do report that severe pain was marginally associated with worsening memory tests [16]. It remains questionable whether these marginal changes are also clinically valuable.

C-reactive protein and the pain-cognition relationship

Given the longitudinal association between severe pain and memory impairment, we were interested in clarifying a possible mechanism, which might lead to new treatment strategies for individuals suffering from pain and at risk for cognitive decline. Moriarty and colleagues suggest that pain seems to be associated with a change in several neurotransmitters [2], including the release of pro-inflammatory cytokines during pain, which may affect cognitive functioning. However, we could not establish a mediating role of CRP in the association between severe pain and cognition in the Health and Retirement Study (*chapter 6*). In contrast to previous findings [2] we did not find a significant cross-sectional association between pain and cognition after adjusting for multiple covariates. This might be due to overadjustment in our multivariate models since other studies often did not adjust for all these possible confounders [2]. It is also possible that other studies would not have found significant results after adjusting for all these variables, since they might actually be real confounders in the pain-cognition relationship. It is also in contrast with our previous findings in the MOBILIZE data, where the association between pain interference and memory and general cognitive performance was significant (*chapter 2*). However, several of these associations described in *chapter 2* between pain and specific cognitive domains also disappeared after adjusting for multiple confounders, suggesting that not pain but other factors are contributing to cognitive impairment. Alternatively, the possible effects of inflammation (caused by pain) on cognition need time to develop, since a few studies have shown that pain affects cognition over time [7,17].

Neither did we find an association between CRP and cognition, which is also in contrast with previous studies, showing an association between chronic inflammation and alzheimer's disease [18] and between levels of peripheral CRP and cognitive decline, although this association was weak [19].

Pain and the Motoric Cognitive Risk Syndrome (MCR)

Previous studies have shown already that pain in older adults is associated with slow gait [20] and cognitive impairment [2,4,17], which is in line with our results showing that older adults with severe pain have a higher incidence of MCR *(chapter 7)*. Older adults with severe pain also had an increased risk of prevalent MCR, compared to those without pain, after adjusting for demographic, peripheral, central or biological risk factors. To our knowledge, this is the first study analyzing the association between pain and MCR.

Concluding remarks

Both our results and the results of earlier studies show a mixed picture of the potential association between pain and cognition. Two possible factors, diminished attention and elevated CRP, that could explain how pain may affect cognition have been described above. Other possible mechanisms have been studied, for instance cognitive decline caused by stress. Neuroimaging studies have shown that pain is associated with a shrinkage of the hippocampus [21] and decreased gray matter volumes, such as in the cingulate cortex, insula and dorsolateral prefrontal cortex [22-24], which are key structures for cognition. Such a mechanism could account for the longitudinal association between pain and incident memory impairment and MCR. Another theory how pain may affect cognition directly, is that pain causes stress and that this results in cognitive decline via putative cortisol based pathways [25,26] similar to other stressful exposures [27,28].

Methodological considerations

In the previous chapters, we have already addressed several methodological limitations. In this section, we will discuss limitations of our research in general.

Assessment of pain

In the CCMA and HRS samples, duration of pain was not included. Therefore, we cannot state that we have studied chronic pain. The presence of chronic pain is often not evaluated directly. Other researchers in this field have tried to use other definitions of pain referring to chronic pain, including persistent pain (in two subsequent data waves) [7] or just avoid specifying the duration of pain, since information about chronicity of pain was not included in the questionnaires [16,29]. Also, some pain instruments have been developed or validated to measure chronic nonmalignant pain, such as the Brief Pain Inventory [30] and the McGill Pain Questionnaire Short Form [6,31], while the duration of pain for at least 3 months was not included in these questionnaires.

Until recently, pain was not categorized in a systematic manner, which has made the interpretation of chronic pain related epidemiological research difficult [32]. In the International Classification of Diseases 11th Revision (ICD-11), a code for chronic pain has been proposed for the first time. The ICD-11 will come into effect in 2022. In many countries ICD codes are used for coding diagnoses and to report diseases and comorbidities in clinical research. In cooperation with the WHO, an IASP working group developed a classification system of chronic pain, where chronic pain is defined as pain persisting or recurring for more than 3 months. The system includes one code for “chronic primary pain” and six codes for chronic secondary pain syndromes. In other words, pain can be defined as a sole or leading complaint (in conditions as

fribromylagia or non-specific low-back pain) or secondary to an underlying disease [33,34]. Next, besides duration of pain, neither were pain locations or types of pain included in our datasets.

Assessment of cognition
The cognitive tests in the different samples were not the same, and therefore the results cannot be compared with each other. On the other hand are there multiple neuropsychological tests that are validated to measure a similar domain of cognitive functioning.

Next, some tests were challenging for older adults, including the Visual Elevator test, measuring attentional switching. This resulted in a relatively high number of incomplete tests on this subscale of the Test of Everyday Attention (TEA), for which we have suggested some textual modifications which probably make the tests easier to understand, in *chapter 3*, that should be evaluated in future research.

Use of observational data
An important limitation is that we used data from observational studies for all our analyses. Therefore, no conclusions can be drawn about the causal relationship between pain and cognitive functioning. However, the threshold effect of pain severity on incident cognitive impairment might support a causal relationship between pain and cognition, since increasing severity of pain influences the outcome (impaired cognitive functioning). However, only randomized clinical trials could really investigate a causal relationship.

In our analyses, we have excluded participants with severe cognitive impairment, because they might underreport pain severity. Therefore, our results cannot be generalized to older adults with severe cognitive impairment. Older adults with dementia may express their pain differently and assessment tools might be different in people with dementia and should be further validated [35,36].

Statistical methods
To our knowledge, we have used appropriate statistical methods to analyze our data and answer our research questions. We have used linear regression models to study the cross-sectional associations between pain and several domains of cognition. In *chapter 3*, it might have been better to have conducted a factor analysis to test convergent validity of the TEA in adults aged 80 years and older. However, since only some subscales of the TEA were included in our dataset, we were limited to establishing correlations between tests. In *chapter 6* we used path analyses to evaluate the possible mediating role of CRP in the pain-cognition relationship. This is an appropriate statistical method

to test mediation. It might have been better to test the association between pain and cognition first, since this association was not significant anymore after adjusting for multiple possible confounders. However, our analyses were hypothesis based and the assumed associations between the independent, mediator and dependent variables were plausible, based on previous literature and our research.

Clinical implications

Our research has contributed to the theoretical knowledge about the association between pain and cognition in older adults. Clarification of this relationship is an important step and the base for further research looking into the questions how to improve surveillance of cognitive impairment in risk groups, improve cognitive functioning and prolong independence in community-dwelling older adults. However, this is beyond the scope of our research.

With an aging population, health care providers will all face more patients with age-related symptoms and diseases including pain. Given the association between –especially severe- pain and cognition, health care providers evaluating patients with pain may want to take in mind that pain could affect cognition. They may want to make sure that the patient has understood the instructions that were provided. Also, keeping in mind the longitudinal association between pain and memory and MCR, health care providers might be more aware of possible changes in memory and cognition. Patients could be referred for further neuropsychological assessments in case of uncertainty about cognitive performance. This could probably lead to an earlier detection of people with cognitive decline. On the other hand, the question rises whether the cognitive performance of people who are experiencing pain while making the tests, are worse compared to performing these test when they do not experience pain. Since our results support the theory that pain demands attention and this takes precedence over other attention-demanding tasks, it is possible that poorer cognitive performance is only temporary and might improve when the pain is treated. This should be investigated in future research. Also, our longitudinal analyses suggest that the association between pain and impaired cognition is not only temporary. At least we found that older adults with severe pain had a higher risk of developing memory impairment and MCR.

Future research

The most important question remains if there is a causal relationship between (severe) pain and subsequent cognitive impairment and whether treatment of pain leads to improved cognitive functioning. Rodriguez-Raecke and colleagues reported that gray matter decrease in chronic pain patients might at least be partially reversible when pain is successfully treated [37]. However, this was observed in a small sample so future

research should address this question again in a prospective design with more statistical power. Also clinically relevant outcomes such as independent functioning and cognitive functioning should be studied to investigate whether treatment of pain leads to a reduction of cognitive decline or even improvement in cognitive functioning.

Next, questionnaires measuring chronic pain should include a question on duration of pain to ensure that participants experience chronic pain, i.e. pain with a duration of at least three months.

Also, more longitudinal research is needed, to examine the directionality of the relationships and to replicate our findings. The question rises whether cognitive functioning could also impact pain experience. In other words; is it also conceivable that older adults who experience brain changes because of cognitive decline, may be more vulnerable to pain?

Lastly, cognitive training programs have been shown to be effective in older adults to improve cognitive ability, protect against self-reported impairments in instrumental activities of daily living, depressive symptoms and clinically relevant decline in health-related quality of life [38,39]. Future research should evaluate whether these programs are also effective in older adults with pain.

In conclusion

We must conclude that the association between pain and cognition is complex. We found a somewhat mixed picture of the potential association between pain and cognitive performance in older adults. Cross-sectionally, pain is associated with impaired memory, impaired specific domains of attention, and impaired general cognitive performance, after adjustments for multiple confounders. Our analyses also showed longitudinal inversed associations between severe pain and memory and MCR. However, it is also possible that cognitive impairment among those with pain is caused by factors associated with both pain and poor cognition.

We found some evidence that factors associated with increased pain severity, e.g. depression and pain medications, partly explain the association between pain and cognition. We were not able to identify whether inflammation mediates this association. We suggest that health care providers keep in mind that older adults with pain have a higher risk of being cognitively impaired. More research is needed to study the associations between pain and cognition further and to investigate whether pain is a modifiable risk factor for cognitive impairment in older adults.

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SUMMARY

Summary

Introduction

Chronic pain is frequently reported in older adults and the prevalence will only increase with the rising number of older adults as a result of the baby-boom generation. Chronic pain has been associated with falls, functional impairment and poor self-rated health and can have detrimental effects on daily functioning. Also, several mostly cross-sectional studies found an association between chronic pain and impaired cognitive functioning. However, these studies were often performed in small samples, or were restricted to limited domains of cognitive functioning and longitudinal studies are lacking. We used data from three independent prospective cohort studies to analyze the association between pain and multiple domains of cognition and to analyze the temporality and a possible mechanism of this relationship. The aim of these studies was to clarify the association between pain and several domains of cognitive functioning in older adults, which may shed light on potentially modifiable risk factors for cognitive impairment in aging.

Pain and cognition cross-sectionally

The cross-sectional associations between pain and multiple cognitive domains (attention, executive functioning, memory, and general cognitive performance) are described in *chapter 2*. We found that pain severity was associated with impaired memory, executive functioning, and general cognitive performance and pain interference (with daily activities) with impaired attention, memory, executive functioning and general cognitive performance, after adjustments for age, gender, race and education. However, many of these associations were not statistically significant anymore after additional adjustments for chronic conditions and psychiatric medications. So it might be possible that not pain, but factors associated with pain, cause the changes in cognition. The association between pain interference and memory and general cognitive performance in older adults persisted, even after adjusting for demographics, chronic conditions, behaviors, and psychiatric medication.

We also found that the observed relationships between pain and cognitive performance were partly explained by the effect of pain on attentional resources. Therefore we focused on the association between pain and attention in the next chapters. First we found that the Test of Everyday Attention (TEA), which was only validated to measure attention in adults 18-80 years old, is also a valuable tool to measure attention in the very old (*chapter 3)*. However, the Visual Elevator Test, which measures the domain of attentional switching, was the most challenging test for these older participants. In *chapter 4* we showed that higher pain severity was associated with poorer scores in measures of selective and

sustained attention. Pain interference scores were also significantly inversely associated with selective attention. These cross-sectional results in the previous chapters suggest that pain demands attention and takes precedence over other attention-demanding cognitive tasks.

Pain and cognition longitudinally

Longitudinal studies about the associations between pain and multiple domains of cognition are mostly lacking. In *chapter* 5, we found that the presence of severe pain at baseline increases the risk of developing incident memory impairment in older adults in our study. We found no associations between pain and incident attention or executive functioning impairments.

Potential mechanism

Previous studies suggest that pain is associated with a change in several neurotransmitters, including the release of pro-inflammatory cytokines (such as C-reactive protein) during pain, which may affect cognitive functioning. However, the possible mediating role of inflammation has not been reported before. In *chapter 6*, our aim was to study if CPR plays a mediating role in the association between severe pain and cognition. The association we found between severe pain and impaired cognition was not significant anymore after adjustment for several possible confounders and therefore we were not able to establish a possible mediating role of CRP.

Pain and MCR

Finally, in *chapter* 7, we analyzed the cross-sectional and longitudinal associations between pain and the Motoric Cognitive Risk Syndrome (MCR). MCR is a pre-dementia syndrome, characterized by slow gait and subjective cognitive complaints in the absence of dementia and mobility disability. We found that older adults with severe pain had an increased risk of prevalent MCR, compared to those without pain, after adjusting for demographic, peripheral, central or biological risk factors. However, after adjusting for all possible confounders together, the association between severe pain and MCR was not significant anymore, though in the same positive direction. Also, in an independent cohort, we showed that older adults with severe pain had a more than five times increased risk of developing incident MCR, compared to those without pain.

Discussion

This thesis ends with a general discussion (*chapter 8)*, where the findings of *chapter 2* to *chapter 7* are resumed and discussed. To conclude, the association between pain and cognition is complex. Cross-sectionally, pain is associated with impaired memory, impaired specific domains of attention, and impaired general cognitive performance,

after adjustments for multiple confounders. Longitudinally, severe pain is associated with incident memory impairment and incident MCR. However, it is also possible that cognitive impairment in pain patients is caused by factors associated with both pain and poor cognition. We were not able to establish the possible mediating role of CRP in the pain-cognition relationship. Two important limitations of our studies are the use of observational data and the fact that the duration of experiencing pain for three months or longer was not included in the pain questionnaires we have used.

Health care providers evaluating patients with pain should be aware of the possible changes in cognition and might refer patients for further neuropsychological assessments in case of uncertainty about cognitive performance.

Future research should evaluate whether cognitive impairment in pain patients is reversible and whether treatment of pain leads to improved cognitive functioning.

NEDERLANDSE SAMENVATTING

Nederlandse Samenvatting

Introductie

Chronische pijn is een veel voorkomende klacht bij ouderen en de prevalentie van chronische pijn zal alleen maar stijgen met het toenemende aantal ouderen als gevolg van de baby-boom generatie en de toenemende levensverwachting. Chronische pijn is geassocieerd met vallen, verminderd functioneren, een slechte subjectieve gezondheid en belemmeringen in het dagelijkse functioneren. Daarnaast is in enkele onderzoeken een associatie gevonden tussen chronische pijn en verminderd cognitief functioneren. Deze onderzoeken zijn meestal cross-sectioneel van aard, hebben een kleine studiepopulatie, of beperkten zich tot een enkel domein van cognitief functioneren. Voor onze analyses hebben we gebruik gemaakt van data van drie onafhankelijke prospectieve cohort studies om daarmee de cross-sectionele en longitudinale associaties tussen pijn en verschillende domeinen van cognitief functioneren te analyseren en een mogelijk mechanisme te onderzoeken dat de relatie tussen pijn en cognitief functioneren kan verklaren. Het doel van onze analyses is het verhelderen van de associaties tussen pijn en cognitief functioneren, wat mogelijk nieuw licht werpt op potentieel modificeerbare risicofactoren voor cognitieve achteruitgang bij ouderen.

De cross-sectionele associatie tussen pijn en cognitief functioneren

In *hoofdstuk 2* hebben we de cross-sectionele associatie tussen pijn en meerdere domeinen van cognitief functioneren (aandacht, uitvoerende taken, geheugen en algeheel cognitief functioneren) geanalyseerd.

We hebben gevonden dat de ernst van de pijn is geassocieerd met verminderd functioneren op het gebied van geheugen, uitvoerende taken en algeheel cognitief functioneren en dat pijn die interfereert met dagelijks functioneren is geassocieerd met verminderd functioneren op het gebied van aandacht, geheugen, uitvoerende taken en algeheel cognitief functioneren, na correctie voor leeftijd, geslacht, ras en opleiding. Echter, na extra correctie voor chronische condities en medicatie (met een mogelijke invloed op cognitief functioneren) waren een deel van deze associaties niet meer significant. Het is dus mogelijk dat niet pijn, maar factoren geassocieerd met pijn en/of cognitief functioneren, de veranderingen in cognitief functioneren veroorzaken. De associatie tussen pijn die interfereert met dagelijkse activiteiten en geheugen en algeheel cognitief functioneren persisteerde na correctie voor alle bovengenoemde mogelijke confounders.

We vonden ook aanwijzingen dat de relatie tussen pijn en cognitief functioneren deels werd verklaard door aandacht, met andere woorden: pijn vergt aandacht wat kan resulteren in verminderde aandacht tijdens het maken van een test. Daarom richtten we

ons in de volgende hoofdstukken op de associatie tussen pijn en aandacht. Allereerst hebben we gevonden dat de 'Test of Everyday Attention' (TEA), die gevalideerd was om aandacht te meten in personen tussen de 18 en de 80 jaar, ook een valide instrument is om aandacht te meten bij ouderen van 80 jaar en ouder (*hoofdstuk 3*). In *hoofdstuk 4* hebben we laten zien dat de ernst van de pijn is geassocieerd met verminderde selectieve en volgehouden aandacht. Daarnaast vonden we dat pijn die interfereert met dagelijkse activiteiten ook geassocieerd is met verminderde selectieve aandacht. Deze resultaten doen vermoeden dat pijn aandacht vraagt en dat dit concurreert met andere cognitieve taken die aandacht vergen.

De longitudinale associatie tussen pijn en cognitief functioneren

Longitudinale studies over de relatie tussen pijn en verschillende domeinen van cognitief functioneren, ontbreken. In *hoofdstuk 5* laten we zien dat ernstige pijn het risico op het ontstaan van geheugenproblemen verhoogt. We vonden geen longitudinale associatie tussen pijn en een verminderde functie van uitvoerende taken of aandacht.

Mogelijk mechanisme

In eerder onderzoek is een associatie gevonden tussen pijn en veranderingen in bepaalde neurotransmitters, zoals het vrijkomen van pro-inflammatoire cytokines (zoals CRP; 'C-reactive protein') bij pijn, die mogelijk het cognitief functioneren beïnvloeden. Een mediërende rol van inflammatie op de relatie tussen pijn en cognitief functioneren is niet eerder beschreven. In *hoofdstuk 6* was ons doel om de mogelijk mediërende rol van CRP in de relatie tussen ernstige pijn en cognitief functioneren te onderzoeken. De relatie tussen ernstige pijn en cognitief functioneren die we vonden, was echter niet meer significant na correctie voor meerdere mogelijke confounders, waardoor we de mediërende rol van CRP niet konden onderzoeken.

De associatie tussen pijn en MCR

In *hoofdstuk 7* hebben we de cross-sectionele en longitudinale associaties tussen pijn en het 'Motoric Cognitive Risk Syndrome' (MCR) onderzocht. MCR is een pre-dementieel syndroom, dat zich kenmerkt door een langzaam looppatroon en subjectieve cognitieve klachten, zonder dat er sprake is van dementie of mobiliteitsproblemen. We vonden dat ouderen met ernstige pijn een grotere kans hebben dat ze tevens de diagnose MCR hebben, in vergelijking met ouderen zonder pijn, zelfs na correctie voor demografische, perifere, centrale of biologische risicofactoren. Echter, na correctie voor al deze mogelijke confounders tegelijkertijd, was de associatie tussen pijn en MCR niet meer significant, maar wel in dezelfde positieve richting. In een onafhankelijk cohort laten we zien dat ouderen met ernstige pijn een meer dan vijf maal verhoogd risico hebben op het ontwikkelen van MCR, vergeleken met ouderen zonder pijn.

Discussie

Dit proefschrift eindigt met een algemene discussie (*hoofdstuk 8*), waarin we de bevindingen van de hoofdstukken 2 tot en met 7 hebben besproken. We concluderen dat de relatie tussen pijn en cognitief functioneren complex is. Cross-sectioneel is pijn geassocieerd met verminderd geheugen, verschillende specifieke vormen van aandacht en verminderd algeheel cognitief functioneren, na correctie voor meerdere confounders. Longitudinaal is ernstige pijn geassocieerd met het ontwikkelen van geheugen problemen en het MCR syndroom. Het is echter ook mogelijk dat de cognitieve achteruitgang bij mensen met pijn wordt veroorzaakt door factoren die samenhangen met pijn en cognitief functioneren (zoals depressie of medicatie). De mogelijke mediërende rol van CRP in de relatie tussen pijn en cognitief functioneren hebben we niet kunnen bepalen. Beperkingen in ons onderzoek zijn het gebruik van observationele data en het feit dat in de pijn vragenlijsten niet een duur van de pijn van minimaal drie maanden opgenomen is, zodat we niet zeker zijn of de deelnemers chronische pijn hebben.

Zorgverleners die oudere patiënten behandelen met chronische pijn, moeten zich bewust zijn van mogelijke veranderingen in het cognitief functioneren van deze patiëntengroep en kunnen overwegen deze ouderen te verwijzen voor neuropsychologisch onderzoek bij twijfel over het cognitief functioneren. Toekomstig onderzoek kan mogelijk uitwijzen of verminderd cognitief functioneren bij ouderen met pijn reversibel is en of behandeling van pijn leidt tot een verbetering van het cognitief functioneren.

DANKWOORD

Dankwoord

Het is zover, het proefschrift is klaar. Toen ik acht jaar geleden naar Boston ging om onderzoek te doen had ik nooit gedacht dat het zover zou komen. Dit was natuurlijk niet gelukt zonder hulp en steun van anderen die ik daar graag voor wil bedanken.

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Dear Joe, I'm very honoured and grateful for the opportunity you gave me to work with you for two years. I got to know you as a gentle, kind person, strong leader, very approachable and somebody with a great sense of humor. You taught me to be responsible, while you kept an eye on the bigger picture. Besides work, family, friends and good food are important to you, and I'll always remember the Thanksgiving celebration with all these 'ingredients' combined. When we first met, you told me surprised about a Dutch geriatrician who obtained her PhD and published all the papers in one book. Well, here you go again.

Suzanne, after medical school I was pleased to work with you at Umass in Boston. You introduced me to this very interesting and fascinating topic of pain and cognitive functioning. I appreciate all the time you took to review the analyses and papers. Also the visits to your mom, your home, and Thanksgiving celebration with a turkey, are memories that I cherish.

Leden van de promotiecommissie: Prof.dr. M. Huisman, Dr. M. Smalbrugge, prof.dr. M.G.M. Olde Rikkert, prof.dr. J. Gussekloo, Dr. M. Rijsdijk; Dank voor de bereidheid om zitting te nemen in de promotiecommissie en uw kritische beoordeling van het manuscript.

Dear colleagues from Albert Einstein College of Medicine; it was great to work with you. Emma, thanks for your help with my research and the Turkish-Indian-Dutch dinners together with Sanish. Also a special thanks to Helena, Claudene, Mirnova and Donna.

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LIST OF PUBLICATIONS

List of publications

1. The association between pain and prevalent and incident motoric cognitive risk syndrome in older adults.
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ABOUT THE AUTHOR

About the author

Guusje van der Leeuw was born on June 16th 1988 in Geleen, The Netherlands. She followed secondary school at 'het Sint Maartens College Maastricht', from which she gratuated in 2006 and obtained her VWO Gymnasium diploma. In this year she moved to Utrecht to start medical school at Utrecht University.

During medical school, Guusje conducted research internships at the department of General Practice of the Amsterdam UMC, location VUMC. In between her bachelor and master degree, she obtained a minor in French Language and Culture at Utrecht University.

After graduating medical school in 2013, she moved to Boston to perform research at the Univerisity of Massachussetts under supervision of prof. S.G. Leveille. She returned to the Netherlands in 2014 to work at the department of Neurology (Tergooi hospital, Blaricum), and Pyschiatry (Altrecht, Utrecht). In March 2016, she started her training to become a general practitioner at the Amsterdam UMC, location VUMC. One year later she also entered a PhD trajectory and since then combined clinical work and scientific research. In March 2017, she moved to New York (NY, USA), where she performed research at Albert Einstein College of Medicine, the Bronx, under supervision of prof.dr. J. Verghese, prof.dr. H.E. van der Horst and dr. A.H. Blankenstein.

Guusje is living in Amsterdam together with her husband Koen van der Mijn and their two children Mila and Tobias.