

Research Article

# Pain and Cognitive Function 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 elderly 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 (MOBILIZE) Boston Study, a population-based study of persons aged 70 and older. Global pain severity and interference were 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 adults 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 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.

**Key Words:** Pain—Cognitive function—Aging—Epidemiology—Neuropsychology

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 people (6,7). Noncancer 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 depend 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 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 nonmalignant 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 (eg, 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 (eg, 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 HVLT 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 HVLT (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 five tests, representing seven variables. We used HVLT total and delayed recall, TMT Parts A and B, phonemic (FAS 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 substudy 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 (38). 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 elderly adults, 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 ( $\leq 12$  years of education) and 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 earlier, 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 nontransformed data did not differ from each other. Therefore we report only the analyses using nontransformed 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 U.S. 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  $\geq 4$  on the BPI interference subscale) and 38% reported zero interference from pain. Average pain severity and interference scores are displayed according to the demographic characteristics in Table 1. Older adults with more severe pain or more pain interference were more likely to be women, African American race and had fewer years of education.

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

**Table 1.** Demographic Characteristics According to Pain Severity and Pain Interference Among 765 Adults Aged 70 Years and Older, MOBILIZE Boston Study

Characteristic	Total Sample	Brief Pain Inventory			
		Pain Severity Mean (SD)	<i>p</i> Value*	Pain Interference Mean (SD)	<i>p</i> Value*
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)	

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

the cognitive tests within the executive function and memory domains, except for Letter Fluency (Tables 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 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.

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 HVLIT 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 earlier, 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 is involved in chronic pain (49). The prefrontal cortex is crucial for many higher brain functions such as representation and execution of actions, goal-oriented behavior 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,

**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
Memory	Letter Fluency	-1.11 (0.24)	≤.001	-0.39 (0.23)	.086	-0.38 (0.24)	.112
	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 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
Memory	Letter Fluency	-0.92 (0.24)	≤.001	-0.31 (0.22)	.150	-0.36 (0.24)	.146
	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 SE from general linear regression models.

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 (eg, TMT (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 earlier (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 elderly people 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 undertreatment 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 health care 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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## Conflict of Interest

None declared.

## References

- Centers for Disease Control and Prevention (CDC). Public health and aging: projected prevalence of self-reported arthritis or chronic joint symptoms among persons aged >65 years—United States, 2005–2030. *MMWR Morb Mortal Wkly Rep.* 2003;52:489–491.
- Elliott AM, Smith BH, Penny KI, Smith WC, Chambers WA. The epidemiology of chronic pain in the community. *Lancet.* 1999;354:1248–1252.
- Edwards RR. Age differences in the correlates of physical functioning in patients with chronic pain. *J Aging Health.* 2006;18:56–69.
- Lichtenstein MJ, Dhanda R, Cornell JE, Escalante A, Hazuda HP. Disaggregating pain and its effect on physical functional limitations. *J Gerontol A Biol Sci Med Sci.* 1998;53:M361–M371.
- Shah RC, Buchman AS, Boyle PA, et al. Musculoskeletal pain is associated with incident mobility disability in community-dwelling elders. *J Gerontol A Biol Sci Med Sci.* 2011;66:82–88. doi:10.1093/gerona/glq187
- Ettinger WH Jr, Fried LP, Harris T, Shemanski L, Schulz R, Robbins J. Self-reported causes of physical disability in older people: the Cardiovascular Health Study. CHS Collaborative Research Group. *J Am Geriatr Soc.* 1994;42:1035–1044.
- Leveille SG, Fried L, Guralnik JM. Disabling symptoms: what do older women report? *J Gen Intern Med.* 2002;17:766–773.
- Shega JW, Weiner DK, Paice JA, et al. The association between noncancer pain, cognitive impairment, and functional disability: an analysis of the Canadian study of health and aging. *J Gerontol A Biol Sci Med Sci.* 2010;65:880–886. doi:10.1093/gerona/glq039
- Cahn-Weiner DA, Farias ST, Julian L, et al. Cognitive and neuroimaging predictors of instrumental activities of daily living. *J Int Neuropsychol Soc.* 2007;13:747–757. doi:10.1017/S1355617707070853
- Royall DR, Palmer R, Chiodo LK, Polk MJ. Declining executive control in normal aging predicts change in functional status: the Freedom House Study. *J Am Geriatr Soc.* 2004;52:346–352.
- Royall DR, Palmer R, Chiodo LK, Polk MJ. Normal rates of cognitive change in successful aging: the freedom house study. *J Int Neuropsychol Soc.* 2005;11:899–909.
- Leveille SG, Jones RN, Kiely DK, et al. Chronic musculoskeletal pain and the occurrence of falls in an older population. *JAMA.* 2009;302:2214–2221. doi:10.1001/jama.2009.1738
- Rubenstein LZ. Falls in older people: epidemiology, risk factors and strategies for prevention. *Age Ageing.* 2006;35(suppl 2):ii37–ii41. doi:10.1093/ageing/af084
- Speechley M, Belfry S, Borrie MJ, et al. Risk factors for falling among community-dwelling veterans and their caregivers. *Can J Aging.* 2005;24:261–274.
- Weiner DK, Rudy TE, Morrow L, Slaboda J, Lieber S. The relationship between pain, neuropsychological performance, and physical function in community-dwelling older adults with chronic low back pain. *Pain Med.* 2006;7:60–70. doi:10.1111/j.1526-4637.2006.00091.x
- Apkarian AV, Sosa Y, Krauss BR, et al. Chronic pain patients are impaired on an emotional decision-making task. *Pain.* 2004;108:129–136. doi:10.1016/j.pain.2003.12.015
- Dick BD, Rashid S. Disruption of attention and working memory traces in individuals with chronic pain. *Anesth Analg.* 2007;104:1223–1229, tables of contents. doi:10.1213/01.ane.0000263280.49786.f5
- Grisart JM, Van der Linden M. Conscious and automatic uses of memory in chronic pain patients. *Pain.* 2001;94:305–313.
- Karp JF, Reynolds CF 3rd, Butters MA, et al. The relationship between pain and mental flexibility in older adult pain clinic patients. *Pain Med.* 2006;7:444–452. doi:10.1111/j.1526-4637.2006.00212.x
- Oosterman JM, Derksen LC, van Wijck AJ, Veldhuijzen DS, Kessels RP. Memory functions in chronic pain: examining contributions of attention and age to test performance. *Clin J Pain.* 2011;27:70–75. doi:10.1097/AJP.0b013e3181f15cf5
- Hart RP, Martelli MF, Zasler ND. Chronic pain and neuropsychological functioning. *Neuropsychol Rev.* 2000;10:131–149.
- Eccleston C, Crombez G. Pain demands attention: a cognitive-affective model of the interruptive function of pain. *Psychol Bull.* 1999;125:356–366.
- Rantakokko M, Mänty M, Rantanen T. Mobility decline in old age. *Exerc Sport Sci Rev.* 2013;41:19–25. doi:10.1097/JES.0b013e3182556f1e
- Sturnieks DL, St George R, Lord SR. Balance disorders in the elderly. *Neurophysiol Clin.* 2008;38:467–478. doi:10.1016/j.neucli.2008.09.001
- Escobar JI, Burnam A, Karno M, Forsythe A, Landsverk J, Golding JM. Use of the Mini-Mental State Examination (MMSE) in a community population of mixed ethnicity. Cultural and linguistic artifacts. *J Nerv Ment Dis.* 1986;174:607–614.
- Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189–198.
- Leveille SG, Kiel DP, Jones RN, et al. The MOBILIZE Boston Study: design and methods of a prospective cohort study of novel risk factors for falls in an older population. *BMC Geriatr.* 2008;8:16. doi:10.1186/1471-2318-8-16
- Samelson EJ, Kelsey JL, Kiel DP, et al. Issues in conducting epidemiologic research among elders: lessons from the MOBILIZE Boston Study. *Am J Epidemiol.* 2008;168:1444–1451. doi:10.1093/aje/kwn277
- Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain.* 2004;20:309–318.
- Cleeland C. Measurement of pain by subjective report. In: Chapman C, Loeser F, eds. *Advances in Pain Research and Therapy. Vol. 12: Issues in Pain Measurement.* New York, NY: Raven Press; 1989:391–403.
- Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the brief pain inventory for chronic nonmalignant pain. *J Pain.* 2004;5:133–137. doi:10.1016/j.jpain.2003.12.005
- Tombaugh TN. Trail making test A and B: normative data stratified by age and education. *Arch Clin Neuropsychol.* 2004;19:203–214. doi:10.1016/S0887-6177(03)00039-8
- Lezak M. *Neuropsychological Assessment.* 4th ed. New York, NY: Oxford University Press; 2004.
- Ble A, Volpato S, Zuliani G, et al. Executive function correlates with walking speed in older persons: the InCHIANTI study. *J Am Geriatr Soc.* 2005;53:410–415. doi:10.1111/j.1532-5415.2005.53157.x
- Drane DL, Yuspeh RL, Huthwaite JS, Klingler LK. Demographic characteristics and normative observations for derived-trail making test indices. *Neuropsychiatry Neuropsychol Behav Neurol.* 2002;15:39–43.
- Eggermont LH, Milberg WP, Lipsitz LA, Scherder EJ, Leveille SG. Physical activity and executive function in aging: the MOBILIZE Boston Study. *J Am Geriatr Soc.* 2009;57:1750–1756. doi:10.1111/j.1532-5415.2009.02441.x
- Pugh KG, Kiely DK, Milberg WP, Lipsitz LA. Selective impairment of frontal-executive cognitive function in African Americans with cardiovascular risk factors. *J Am Geriatr Soc.* 2003;51:1439–1444.
- Grande L, Milberg W, Rudolph J, Gaziano M, McGlinchey R. A timely screening for executive functions and memory. *J Int Neuropsychol Soc.* 2005;11:9–10.
- Chester JG, Grande LJ, Milberg WP, McGlinchey RE, Lipsitz LA, Rudolph JL. Cognitive screening in community-dwelling elders: performance on the clock-in-the-box. *Am J Med.* 2011;124:662–669. doi:10.1016/j.amjmed.2011.02.023
- Brandt J. The Hopkins Verbal Learning Test: development of a new verbal memory test with six equivalent forms. *Clin Neuropsychol.* 1991;5:125–142.
- Glisky EL, Kong LL. Do young and older adults rely on different processes in source memory tasks? A neuropsychological study. *J Exp Psychol Learn Mem Cogn.* 2008;34:809–822. doi:10.1037/0278-7393.34.4.809
- Wechsler D, ed. *Wechsler Adult Intelligence Test.* New York, NY: The Psychological Corporation; 1981.
- Gross AL, Mungas DM, Crane PK, et al. Effect of education and race on cognitive decline: Does research study membership matter? *Psychology and Aging.* In press.
- Gross AL, Jones RN, Inouye SK. Development of an expanded measure of physical functioning for older persons in epidemiologic research. *Res Aging.* 2014;37:671–694. doi: 10.1177/0164027514550834

45. Gross AL, Sherva R, Mukherjee S, et al. Calibrating longitudinal cognition in Alzheimer's disease across diverse test batteries and datasets. *Neuroepidemiology*. 2014;43:194–205. doi:10.1159/000367970
46. Langa KM, Plassman BL, Wallace RB, et al. The aging, demographics, and memory study: study design and methods. *Neuroepidemiology*. 2005;25:181–191. doi:87448 [pii]
47. Jones RN, Gallo JJ. Education and sex differences in the mini-mental state examination: effects of differential item functioning. *J Gerontol B Psychol Sci Soc Sci*. 2002;57:P548–P558.
48. Valet M, Sprenger T, Boecker H, et al. Distraction modulates connectivity of the cingulo-frontal cortex and the midbrain during pain—an fMRI analysis. *Pain*. 2004;109:399–408. doi:10.1016/j.pain.2004.02.033
49. Apkarian AV, Thomas PS, Krauss BR, Szeverenyi NM. Prefrontal cortical hyperactivity in patients with sympathetically mediated chronic pain. *Neurosci Lett*. 2001;311:193–197.
50. Miller EK. The prefrontal cortex and cognitive control. *Nat Rev Neurosci*. 2000;1:59–65. doi:10.1038/35036228
51. Fuster JM. The prefrontal cortex—an update: time is of the essence. *Neuron*. 2001;30:319–333.
52. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu Rev Neurosci*. 2001;24:167–202. doi:10.1146/annurev.neuro.24.1.167
53. Munakata Y, Herd SA, Chatham CH, Depue BE, Banich MT, O'Reilly RC. A unified framework for inhibitory control. *Trends Cogn Sci*. 2011;15:453–459. doi:10.1016/j.tics.2011.07.011
54. Bechara A. The neurology of social cognition. *Brain*. 2002;125(Pt 8):1673–1675.
55. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci*. 2002;3:655–666. doi:10.1038/nrn894
56. Mesulam MM. From sensation to cognition. *Brain*. 1998;121(Pt 6):1013–1052.
57. Saper CB. The central autonomic nervous system: conscious visceral perception and autonomic pattern generation. *Annu Rev Neurosci*. 2002;25:433–469. doi:10.1146/annurev.neuro.25.032502.111311
58. Zimmerman ME, Pan JW, Hetherington HP, Lipton ML, Baigi K, Lipton RB. Hippocampal correlates of pain in healthy elderly adults: a pilot study. *Neurology*. 2009;73:1567–1570. doi:10.1212/WNL.0b013e3181c0d454
59. Head D, Rodrigue KM, Kennedy KM, Raz N. Neuroanatomical and cognitive mediators of age-related differences in episodic memory. *Neuropsychology*. 2008;22:491–507. doi:10.1037/0894-4105.22.4.491
60. Golomb J, Kluger A, de Leon MJ, et al. Hippocampal formation size in normal human aging: a correlate of delayed secondary memory performance. *Learn Mem*. 1994;1:45–54.
61. Van Petten C. Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. *Neuropsychologia*. 2004;42:1394–1413. doi:10.1016/j.neuropsychologia.2004.04.006
62. Petersen RC, Jack CR Jr, Xu YC, et al. Memory and MRI-based hippocampal volumes in aging and AD. *Neurology*. 2000;54:581–587.
63. Iezzi T, Duckworth MP, Vuong LN, Archibald YM, Klinck A. Predictors of neurocognitive performance in chronic pain patients. *Int J Behav Med*. 2004;11:56–61. doi:10.1207/s15327558ijbm1101\_7
64. Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: a review of clinical and preclinical research. *Prog Neurobiol*. 2011;93:385–404. doi:10.1016/j.pneurobio.2011.01.002
65. Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J Am Geriatr Soc*. 2012;60:2127–2136. doi:10.1111/j.1532-5415.2012.04209.x
66. Byrd DA, Sanchez D, Manly JJ. Neuropsychological test performance among Caribbean-born and U.S.-born African American elderly: the role of age, education and reading level. *J Clin Exp Neuropsychol*. 2005;27:1056–1069. doi:10.1080/13803390490919353
67. Acevedo A, Loewenstein DA, Agrón J, Duara R. Influence of sociodemographic variables on neuropsychological test performance in Spanish-speaking older adults. *J Clin Exp Neuropsychol*. 2007;29:530–544. doi:10.1080/13803390600814740
68. Avila R, Moscoso MA, Ribeiz S, Arrais J, Jaluul O, Bottino CM. Influence of education and depressive symptoms on cognitive function in the elderly. *Int Psychogeriatr*. 2009;21:560–567. doi:10.1017/S1041610209008928
69. Mungas D, Reed BR, Farias ST, Decarli C. Age and education effects on relationships of cognitive test scores with brain structure in demographically diverse older persons. *Psychol Aging*. 2009;24:116–128. doi:10.1037/a0013421
70. Ardila A, Ostrosky-Solis F, Rosselli M, Gómez C. Age-related cognitive decline during normal aging: the complex effect of education. *Arch Clin Neuropsychol*. 2000;15:495–513. doi:10.1080/1380339000402 [pii]
71. Farmer ME, Kittner SJ, Rae DS, Bartko JJ, Regier DA. Education and change in cognitive function. The Epidemiologic Catchment Area Study. *Ann Epidemiol*. 1995;5:1–7. doi:104727979400047W [pii]
72. Evans DA, Beckett LA, Albert MS, et al. Level of education and change in cognitive function in a community population of older persons. *Ann Epidemiol*. 1993;3:71–77. doi:1047-2797(93)90012-S [pii]
73. Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. *Clin Geriatr Med*. 2013;29:737–752. doi:10.1016/j.cger.2013.07.002
74. Wilson RS, Hebert LE, Scherr PA, Barnes LL, Mendes de Leon CF, Evans DA. Educational attainment and cognitive decline in old age. *Neurology*. 2009;72:460–465. doi:10.1212/01.wnl.0000341782.71418.6c
75. Zahodne LB, Glymour MM, Sparks C, et al. Education does not slow cognitive decline with aging: 12-year evidence from the victoria longitudinal study. *J Int Neuropsychol Soc*. 2011;17:1039–1046. doi:10.1017/S1355617711001044
76. Farrell MJ, Katz B, Helme RD. The impact of dementia on the pain experience. *Pain*. 1996;67:7–15. doi:0304-3959(96)03041-2 [pii]
77. Corbett A, Husebo B, Malcangio M, et al. Assessment and treatment of pain in people with dementia. *Nat Rev Neurol*. 2012;8:264–274. doi:10.1038/nrneurol.2012.53
78. Eggermont LH, Penninx BW, Jones RN, Leveille SG. Depressive symptoms, chronic pain, and falls in older community-dwelling adults: the MOBILIZE Boston Study. *J Am Geriatr Soc*. 2012;60:230–237. doi:10.1111/j.1532-5415.2011.03829.x
79. Gray SL, Lai KV, Larson EB. Drug-induced cognition disorders in the elderly: incidence, prevention and management. *Drug Saf*. 1999;21:101–122.
80. Wolinsky FD, Unverzagt FW, Smith DM, Jones R, Stoddard A, Tennstedt SL. The ACTIVE cognitive training trial and health-related quality of life: protection that lasts for 5 years. *J Gerontol A Biol Sci Med Sci*. 2006;61:1324–1329.
81. Wolinsky FD, Vander Weg MW, Martin R, et al. The effect of speed-of-processing training on depressive symptoms in ACTIVE. *J Gerontol A Biol Sci Med Sci*. 2009;64:468–472. doi:10.1093/gerona/gln044
82. Pahor M, Guralnik JM, Wan JY, et al. Lower body osteoarticular pain and dose of analgesic medications in older disabled women: the Women's Health and Aging Study. *Am J Public Health*. 1999;89:930–934.