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Authors

Bell, Tyler Reed

Sprague, Briana N

Ross, Lesley A

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Longitudinal Associations of Pain and Cognitive Decline in Community-Dwelling Older Adults

Tyler Reed Bell[*,1], **Briana N. Sprague**[2], **Lesley A. Ross**[3]

[1]Department of Psychiatry, University of California San Diego

[2]Department of Epidemiology, University of Pittsburgh

[3]Department of Psychology, Institute for Engaged Aging, Clemson University

Abstract

Pain is inversely associated with cognitive function in older adults, but the effects of pain on cognitive decline are not fully clear. This study examined the associations of baseline pain, pain persistence, and incident pain with changes in cognition across ten years in a sample of healthy community-dwelling older adults (n = 688; mean age = 74, SD = 6.05) from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial. While ACTIVE was a four-arm single-blind cognitive training randomized controlled trial, the current study includes only participants from the no-contact control group. Pain was examined using the MOS SF-36 and cognitive tests examined simple processing speed, complex processing speed, divided and selective attention, memory, reasoning, and cognitive status. Multilevel models tested the associations of baseline pain, incident pain, and pain persistence on cognitive function and cognitive decline, adjusted for baseline age, time (years after follow-up), race, gender, education, marital status, and depressive symptoms at baseline and over time. Thirty-one percent reported pain at baseline which was related to worse baseline memory and accelerated decline in processing speed. Forty-two percent of older adults reported incident pain had accelerated decline in complex processing speed, divided attention, memory, reasoning, and cognitive status. On average, older adults reported a mean of 2 waves of pain persistence that related to accelerated decline in memory. In sum, pain is common in community-dwelling older adults and is related to accelerated cognitive decline, especially when incident.

[*]Corresponding author. Please contact the corresponding author Tyler Bell for any questions or comments, tylerreedbell@gmail.com, physical address: 3252 Holiday Court Drive, La Jolla, CA., 92122.

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Data relevant to the publication is publicly accessible https://www.icpsr.umich.edu/web/NACDA/studies/36036. Syntax for data preparation and data analyses are publicly available (https://github.com/trbellucsd/ACTIVE-Pain-Cognitive-Decline); analyses were not pre-registered. This work has not been previously presented or published via any other platform. Data relevant to the publication is publicly accessible here: https://www.icpsr.umich.edu/web/NACDA/studies/36036

We certify that this work has not been reported previously. To the best of our knowledge, no studies have comprehensively assessed associations between baseline pain, incident pain, and pain persistence on cognitive decline, especially using a comprehensive battery of tests in community dwelling older adults. Our findings specifically particularly highlight the role of incident pain in accelerating cognitive decline in older adults. Incident pain might serve as an important target to curtail poorer cognition in later life.

Keywords

pain; chronic pain; persistent pain; cognitive decline; older adults

Introduction

The number of older adults living with cognitive impairment is expected to double by 2050, highlighting the urgent need for interventions that delay the onset or slow the progression of cognitive decline (Matthews et al., 2019). One potentially manageable factor is pain, defined as the sensory-affective experience of actual or anticipated tissue damage reported in over 50% of older adults (Patel, Guralnik, Dansie, & Turk, 2013). Clinical and non-clinical studies show that older adults exhibiting even low pain levels have worse processing speed, memory, and problem-solving abilities compared to older adults without pain (van der Leeuw et al., 2018). Similarly, those reporting persistent pain show greater cognitive decline and a twofold greater risk of developing mild cognitive impairment and dementia (Bell, Franz, & Kremen, 2021; Ezzati et al., 2019; Tzeng et al., 2018; van der Leeuw et al., 2018; Whitlock et al., 2017). Clinicians seeking to ameliorate the risk of dementia and maintain cognitive health in older adults will benefit from comprehensive knowledge of how pain relates to cognitive decline.

A major theory has linked pain with cognitive function. The *interruptive model of pain* posits that experiencing pain diverts attentional resources away from cognitive function to pain (Eccleston & Crombez, 1999). In other words, persons with pain do not perform as well as cognitive resources are spent attending to the pain rather than the cognitive task at hand. Neuroimaging has supported this by demonstrating shared neural networks in the salience detection network, which compete for resources to attend pain and cognitive tasks (Legrain, Iannetti, Plaghki, & Mouraux, 2011). The interruptive model of pain posits that pain should worsen cognitive function as it leads to attentional distraction, a result supported in clinical studies (Cherry et al., 2012; Grigsby, Rosenberg, & Busenbark, 1995; Lee et al., 2015; Park, Glass, Minear, & Crofford, 2001; Pulles & Oosterman, 2011; Schiltenwolf et al., 2014). In a non-clinical study of older adults, analyses have highlighted baseline pain (pain reported at the first study assessment) and pain persistence (how many waves one has reported pain) as predictive of cognitive decline (Bell, Franz, & Kremen, 2021). However, results have not yet considered the role of incident pain which involves the occurrence of new cases of pain over time (Bell, Pope, Downer, Barbara, & Crowe, 2021; Dunietz et al., 2018; Park, Cho, Lim, & Kim, 2018).

Like other distractors, the effects of pain on cognitive function would be expected to be strongest near its first occurrence when unexpected. The interruptive model of pain posits that new pain should be most distracting (Eccleston & Crombez, 1999). Studies of pain and cognitive function in older adults have focused mostly on cross-sectional relations to pain or the prospective relationships of baseline and persistent pain. Because the onset of pain is unknown from these measures, little is known about how incident pain relates to cognitive function in older adults and what happens to cognitive change thereafter. The effect of incident pain is important to untangle as newly diagnosed painful conditions have

been shown to increase the risk of dementia by up to over 150% (Tzeng et al., 2018), while a general report of pain, without distinction of whether it is incident or long-standing, relates to only a 20–30% increased risk (Khalid et al., 2021; Yamada et al., 2019).

Of those that have examined incident pain, two studies found that older adults who developed pain after surgery were more likely to have cognitive impairment from three days (Duggleby & Lander, 1994) to 2 years later (Huai et al., 2021), even after that pain subsided and after accounting for the effects of anesthesia. Furthermore, a recent study in community-dwelling Puerto Rican older adults found that incident pain was related to changes in cognitive status (via a dementia screening assessment), whereas persistent pain was not (Bell, Pope, Downer, Barba, & Crowe, 2021). Together, associations suggest that older adults developing incident pain in later life might be at greatest risk for cognitive decline than others with a pre-existing history of pain or no pain. Analyses have yet to explore this while simultaneously considering baseline pain and pain persistence.

The first aim of this study was to describe the frequency and correlates of baseline pain, incident pain, and pain persistence in community-dwelling older adults (Aim 1). This will enhance our understanding of how common pain types are in a healthy sample of older adults and the factors most related. Next, to extend understanding of pain and cognition, we examined the cross-sectional association between baseline pain and baseline cognitive function (Aim 2) and associations of incident pain and pain persistence with concurrent cognitive function, i.e., cognitive function when incident pain or greater pain persistence is first reported (Aim 3). We further examined how baseline pain, incident pain, and greater pain persistence related to the rate of cognitive decline after being reported (Aim 4). Cognitive domains assessed included processing speed, divided attention, selective attention, memory, and reasoning, which are vulnerable to age-related declines (Craik & Bialystok, 2006). We also assessed cognitive status using a dementia screening tool in addition to the specific cognitive domains above. Our central hypothesis was that at the time people first reported pain (at baseline, incident, or as more persistent), they would have lower cognitive function and greater cognitive decline thereafter. Not only is this suggested by general cross-sectional studies of pain and cognitive function (Karp et al., 2006; Oosterman, Derksen, van Wijck, Veldhuijzen, & Kessels, 2011; van der Leeuw et al., 2018) but also recent studies of baseline pain, incident pain, and pain persistence (Bell et al., 2021; Duggleby & Lander, 1994; Huai et al., 2021).

Regarding cognitive domains, we hypothesized that domains requiring high degrees of attention would be most susceptible to disruption, as there are fewer remaining attentional resources to compensate for pain-related distraction. Such a hypothesis is in line with cross-sectional studies and meta-analyses showing that people with painful conditions have more deficits in attention and executive function-related tasks rather than memory (Abeare et al., 2010; van der Leeuw et al., 2016), specifically including divided and selective attention tasks and reasoning (Bell et al., 2018; Berryman et al., 2014; Berryman et al., 2013). As such, we hypothesized that incident pain would be associated with worse divided and selective attention and reasoning performance. Further, as there are some inconsistencies regarding pain conditions and poorer processing speed (Cherry et al., 2012; Grigsby et al., 1995; Lee et al., 2015; Park et al., 2001; Pulles & Oosterman, 2011; Schiltenwolf et

al., 2014), we hypothesized that task demand may impact pain relationships. As such, we explored the association of pain measures and processing speed using tasks of simple (a low-demand task reliant mainly on motor speed) and complex processing speed (a high-demand task measuring speed to make decisions in the face of distracting stimuli). We also explored whether changes in cognitive function could be detected by a cognitive status screener. Previous studies in the Health and Retirement Study have shown that dementia screeners can capture cognitive decline related to pain, but associations with incident pain are particularly unknown (Bell, Franz, Kremen, et al., 2021; Whitlock et al., 2017).

Method

Transparency and Openness

Data relevant to the publication is publicly accessible https://www.icpsr.umich.edu/web/NACDA/studies/36036. Syntax for data preparation and data analyses are publicly available (https://github.com/trbellucsd/ACTIVE-Pain-Cognitive-Decline). Study design, hypotheses, and analyses were not pre-registered.

Design and Participants

This study used the no-contact control participants from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE, ClinicalTrials.gov Identifier NCT00298558) randomized control study. Conducted across six sites in the United States, the ACTIVE study tested the efficacy of three cognitive training programs (vs. a no-contact control) on older adults' cognition and everyday functioning. Recruited from March 1998 to October 1999, participants included adults ages 65 and older who did not present the following exclusion criteria: (1) potential cognitive impairment indicated by MMSE < 23 or reported a diagnosis of dementia; (2) functional impairment (i.e., required extensive assistance with activities of daily living like dressing, bathing, or personal hygiene; Morris & Morris, 1997); (3) self-reported diagnosis of stroke in the last 12 months; (4) self-reported diagnosis of certain cancers and/or current chemo- or radiation therapy; (5) self-reported problems in vision (e.g., difficulty reading news or visual acuity worse than 20/50), hearing, or communication that would prevent full participation in the intervention or outcome assessments; (6) received cognitive training previously; or (7) had been unable to meet time requirements of the study. For this study, we chose to focus on the control group who did not participate in cognitive training (n = 704). Additional details regarding the ACTIVE trial are discussed elsewhere (Jobe et al., 2001).

Of the 704 randomized to the control group, six participants were missing baseline cognitive assessments and an additional 10 participants had missing baseline pain data, leaving an analytic sample of 688 older adults. The analytic sample had a baseline mean age of 74 years (SD = 6.05, range: 65 – 94), were majority woman (73%), White (71%), and widowed or single (62%). On average, participants reported 13.4 years of education (SD = 2.70, range from 6 to 20 years). Further details on the sample are presented in Table 1. Using package "simr" in R version 4.0 (Green & MacLeod, 2016), our sample had a 91% power to detect a fixed effect of at least an f^2 of .01 using mixed linear models.

Procedure

All study procedures were approved by site Institutional Review Boards. After an initial telephone screening, eligible participants provided an in-person informed consent followed by a baseline assessment of surveys and assessments of everyday habits, psychosocial function, health, and physical and cognitive function. Participants were then randomized into one of three training arms or the no-contact control group. All groups completed assessments at immediate posttest and 1, 2, 3, 5, and 10 years after the intervention trial concluded. The current study included participants in the no-contact control group to avoid confounding intervention effects. Additionally, as measures of pain were not administered at the immediate posttest, the current analyses included data from baseline and follow-up assessments from years 1, 2, 3, 5, and 10.

Measures

Pain.—Participants completed the Medical Outcomes Survey SF-36-Item (MOS SF-36) questionnaire (Ware & Sherbourne, 1992). This study used the pain intensity item (Question 21), which asked participants to rate their pain intensity over the prior four weeks on a six-point Likert scale: “None” (1), “Very Mild” (2), “Mild” (3), “Moderate” (4), “Severe” (5), “Very Severe” (6). A cutoff of ≥4 was used to detect clinically-significant pain as done before (Karlson et al., 2020; Landmark, Romundstad, Dale, Borchgrevink, & Kaasa, 2012). *Baseline pain* was defined as the presence of pain intensity ≥4 (4 “Moderate” to 6 “Very Severe”) at the first wave (coded 1) versus <4 (coded 0). Similar to other observational pain studies (Bell, Pope, Fazeli, Crowe, & Ball, 2021; Dunietz et al., 2018; Park, Cho, Lim, & Kim, 2018), *incident pain* was defined as the first instance of reporting pain intensity ≥4 at a follow-up wave (i.e., any assessment post-baseline; coded 1) or not (coded 0). *Pain persistence* was the number of follow-up study waves reporting pain intensity ≥4 after baseline (ranging from 0–5 waves).

Cognitive domains.—Cognitive domains included processing speed, attention, memory, and reasoning performance. *Simple processing speed* was measured via accuracy on the Digit Symbol Substitution Task (DSST; Wechsler, 2008). *Complex processing speed* was measured using the complex reaction time (CRT) task. The CRT is the mean reaction time (ms) to correctly react to road signs without slashes (click mouse for pedestrian or bicycle sign; move mouse to left or right for left and right turn arrows, respectively) and ignore road signs with slashes. Signs are presented in combinations of 3 or 6 signs. The Useful Field of View, or UFOV, test (Ball & Owsley, 1993) was used for divided and selective attention. *Divided attention* was assessed with the UFOV subtest 2 (UFOV2) which involved identifying the central object and locating a peripheral object. *Selective attention* was assessed with UFOV subtests 3 and 4 (UFOV3 and UFOV4). Similar to UFOV2, UFOV3 involved identifying the central object and locating the peripheral object; however, distractor symbols were included. UFOV4 increased in difficulty by including a more complex central identification task while retaining the same peripheral localization task and distractors. *Memory* was assessed using accuracy recall scores on the Hopkins Verbal Learning Task (HVLT; Brandt, 1991), Rey-Auditory Learning Task (AVLT; Lezak, 2004), and the Paragraph Recall subtest (PRT) of the Rivermead Behavioral Memory Test (PRT; Wilson, 1985). All memory tests involve listening to a list of words (HVLT and

AVLT) or a short story and then immediately recalling the information. Scores were the total number of correctly recalled words. *Reasoning* was measured using accuracy on tasks from the Adult Development and Enrichment Project, specifically the Letter Series and Word Series tasks (Blieszner, Willis, & Baltes, 1981). Both tests involve executive function and problem-solving to identify patterns of letters or words.

Scores on time-based measures (CRT, UFOV2, UFOV3, UFOV4) were reverse-scored so that higher scores indicate better performance. Higher scores on all cognitive measures indicate better performance. Cognitive tests were reliably measured within-person over time, with intraclass correlations ranging from .50 to .82. Full details on these measures are provided in Supplemental Information 1.

Cognitive status.—Cognitive status was assessed using the Mini-Mental Status Examination (MMSE; Folstein, 1975), a dementia screening tool that assesses orientation, memory, and math abilities. MMSE scores range from 0 – 30 with higher scores are indicative of better cognitive status. ACTIVE used MMSE performance as an inclusion criterion and excluded participants with scores below 23, which represents cognitive impairment. MMSE scores thus represent the degree of cognitive status originally unimpaired at baseline.

Covariates.—We adjusted for sociodemographic factors typically controlled for in pain studies (Whitlock et al., 2017). These included time-invariant variables of baseline age (years), race (White 1; non-White 0), gender (man 1; woman 0), years of education (range 0 for no education to 20 for doctoral-level or equivalent), and marital status (married/partnered 1; if separated/widowed 0). Baseline depressive symptoms were measured using the total score of the Center for Epidemiologic Studies Depression Scale-12 item (CESD; Radloff, 2016). The CESD asks how often participants experienced 12 depressive symptoms during the previous week from none of the time (0), some of the time (1), much of the time (2), and most or all of the time (3). Higher CESD scores are indicative of greater depressive symptoms. Time-varying depressive symptoms were also included as a covariate to account for concurrent changes in depressive symptoms at later waves (depressive symptoms at follow-up minus baseline depressive symptoms). Time was calculated as years since baseline.

Analysis Plan

For Aim 1, we examined frequency and correlates of baseline pain, incident pain, and pain persistence using 3 general linear models. Eleven two-level multilevel models were conducted to examine associations of baseline pain with baseline cognitive function (Aim 2), incident pain and pain persistence with concurrent cognitive function (Aim 3), and baseline pain, incident pain, and pain persistence with the rate of cognitive decline (Aim 4). Main multilevel models included time defined as years after baseline (age at follow-up minus age at baseline), time-invariant covariates (demographics, baseline depressive symptoms), and time-varying depressive symptoms. The main model is illustrated in Figure 1.

Baseline pain was a time-invariant variable. The main effect evaluated the cross-sectional association of baseline pain with baseline cognitive function ($\gamma 07$); the time interaction

evaluated the association of baseline pain with the rate of cognitive change after baseline (β10). Incident pain was entered as a time-interrupted variable coded 0 at waves before reporting incident pain and 1 at waves thereafter as done in previous studies of event occurrence (Bell, Hill, Bhargava, & Mogle, 2021; Bernal, Cummins, & Gasparrini, 2017). Bernal et al. (2017) provide an in-depth description of this approach. The main effect evaluated the association of incident pain with concurrent cognitive function *when incident pain was first reported* (β3), while the time interaction evaluated the association of incident pain with the rate of cognitive change thereafter (β12; see Bernal, Cummins, & Gasparrini, 2017, for a full description of interrupted time modeling). Pain persistence was included as a time-varying variable centered for baseline pain.

The main effect evaluated the association of reporting one additional wave of pain persistence with concurrent cognitive function (β4) and the time interaction evaluated the association of reporting one additional wave of pain persistence on the rate of cognitive change thereafter (β13). The form of the full multilevel model equation is belolw with three major variable sets:

$$\text{Level 1: } Y_{ij}[\text{Cognitive Test Score}] = [\text{Variable Set 1}] + [\text{Variable Set 2}] + e_{ij}$$

$$\text{Level 2: } \beta 0_i[\text{Baseline Cognitive Test Score}] = [\text{Variable Set 3}] + \mu_i$$

Variable Set 1 . Predictors of Concurrent Cognitive Function: $\beta 0_i + \beta 1(\text{time}_{ij}) + \beta 2(\text{time-varying depressive symptomsij}) + \beta 3\ (\text{incident painij}) + \beta 4(\text{pain persistenceij})$

Variable Set 2. Predictors of Rate of Cognitive Change: $\beta 5(\text{race}_i * \text{time}_{ij}) + \beta 6(\text{gender}_i * \text{time}_{ij}) + \beta 7(\text{education}_i * \text{time}_{ij}) + \beta 8(\text{marital status}_i * \text{time}_{ij}) + \beta 9\ (\text{baseline depressive symptoms}_i * \text{time}_{ij}) + \beta 10(\text{baseline pain}_i * \text{time}_{ij}) + \beta 11\ (\text{time-varying depressive symptoms}_{ij} * \text{time}_{ij}) + \beta 12(\text{incident pain}_{ij} * \text{time}_{ij}) + \beta 13\ (\text{pain persistence}_{ij} * \text{timeij})$

Variable Set 3 . Predictors of Baseline Cognitive Function: $\gamma 00 + \gamma 01\ (\text{baseline age}_i) + \gamma 02(\text{race}_i) + \gamma 03(\text{gender}_i) + \gamma 04(\text{ education}_i) + \gamma 05(\text{marital status}_i) + \gamma 06\ (\text{baseline depressive symptoms i}) + \gamma 07\ (\text{baseline pain i})$

Where Y_{ij} represents the cognitive test score for an individual (i) at each time point (j), $\beta 0_i$ is the baseline cognitive test score for each individual, $\gamma 00$ is the sample mean of the cognitive test scores and $\beta 1$ reflects the yearly rate of change in cognitive test scores tested by our time variable of years after baseline (age at follow-up-age at baseline); $\gamma 1 - 8$ are coefficients estimating the association between demographic and baseline depressive symptoms, and baseline pain with baseline cognition; $\beta 2 - 4$ are coefficients estimating the main effect for one unit higher value in time-varying variables; $\beta 5 - 10$ are coefficients estimating change in cognition as a function of baseline characteristics. The $\beta 11$ coefficient answers whether time-varying depressive symptoms correspond with concurrent cognitive function. Lastly, e_{ij}

and μ_i represent the error within individuals (Level 1 error) and between individuals (Level 2 error), respectively.

Data were analyzed in R version 4.2 using the "lmer" package. Using package "simr" in R version 4.0 (Green & MacLeod, 2016). Effect sizes were estimated using marginal f^2 for each variable, which describes unique variance explained by a multilevel model predictor. F^2 of 02 , .15 , and .35 typically correspond to small, medium, and large effect sizes (Cohen, 1988). Marginal f^2 effect sizes provided using the modTest function from the lme4 add-on packageJwileymisc (https:/cran.r-project.org/web/packages/JWileymisc/index.html). Due to multiple testing, significance testing was evaluated at $\alpha < .01$ for all models. Sensitivity analyses assessed if the number of waves completed confounded results.

Results

Baseline Descriptives and Intercorrelations

Sample descriptives on key study variables at baseline and their intercorrelations are presented in Table 1. Overall, baseline pain was associated with higher education ($r = -.14, p < .001$), identifying as a man ($r = -.11, p = .004$), being windowed/single ($r = -.14, p < .001$), and greater depressive symptoms ($r = .29, p < 001$). Baseline pain was associated with worse simple processing speed on the DSST ($r = -.16, p < .001$), worse complex processing speed ($r = -.11, p = .004$), worse memory on the HVLT task ($r = -.11, p = .003$), worse reasoning on the Letter Series and Word Series tasks (both rs $= -.11, p = .003$).

Aim 1. Frequency and Correlates of Pain

Thirty-one percent ($n = 210$) of older adults reported baseline pain. Forty-two percent ($n = 289$) reported incident pain and the mean pain persistence was 2.25 waves ($SD = 1.25$). Participants were more likely to have baseline pain if they were unmarried ($OR = 2.26$, 95%CI[1.07,4.78]) and had greater baseline depressive symptoms ($OR = 1.24$, 95%CI[1.15,1.33], ps<.01). Incident pain was more likely with time ($OR = 1.22$, 95%[1.08,1.38]) and greater time-varying depressive symptoms ($OR = 1.07$, 95%CI[1.003,1.12], all ps < .01). Greater pain persistence was related to time ($\beta = .07$, 95%CI[.06.11]), being a man ($\beta = .03$, 95%CI%[.001 to .05]), being unmarried ($\beta = .03$, 95%[.01,.05]), and having greater time-varying depressive symptoms ($\beta = .004$, 95%[.001 to .01], all ps < .01).

Aim 2. Pain and Baseline Cognitive Function

Main multilevel models are shown in Table 2 for processing speed, Table 3 for attention, Table 4 for memory, and Table 5 for reasoning and cognitive status. The below results are described for main effects and time interactions, describing associations of variables to baseline cognitive function, concurrent cognitive function, and rate of cognitive change. The main pattern of results is illustrated in Figure 2.

Baseline Pain.—Older adults with baseline pain had better performance on DSST simple processing speed at baseline than older adults without baseline pain ($\beta = .36, p < .001, f^2 = .01$). Baseline pain was also associated with worse performance on AVLT memory ($\beta = -.29, p = .001, f^2 = .004$). There were no significant associations between baseline pain with CRT complex processing speed, divided or selective attention (UFOV 2–4), HVLT or PRT memory, or MMSE ($ps > .01$).

Covariates Effects.—Younger baseline age (βs(|β| s ranged from −.08 to −.02), White race (βs ranged from .31 to .64), more years of education (βs ranged from .04 to .12), and baseline depressive symptoms (βs ranged from −.03 to −.02) were related to higher baseline performance on cognitive test scores, although effects were nonsignificant for some tasks ($ps > .01$, see Table 2 to 5).

Aim 3. Pain and Concurrent Cognitive Function

Incident Pain.—When participants first reported incident pain, they had poorer performance on DSST simple processing speed compared to prior performance ($\beta = -1.43, p < .001, f^2 = .05$), but better performance on CRT complex processing speed ($\beta = .26, p = .009, f^2 = .01$). When participants first reported incident pain, they had better concurrent performance on UFOV2 divided attention compared to prior performance ($\beta = .33, p < .001, f^2 = .02$). Participants also had poorer concurrent performance on AVLT memory compared to prior performance ($\beta = -.27, p = .002, f^2 = .004$). Meanwhile, when participants first reported incident pain, they had better Word Series reasoning ($\beta = .23, p < .001, f = .01$), and Letter Series reasoning ($\beta = .25, p < .001, f^2 = .01$) compared to prior performance. There were no significant associations between incident pain and selective attention (UFOV 3–4), HVLT and PRT memory, or MMSE ($ps > .01$)

Pain Persistence.—When participants reported one additional study wave of pain persistence, they had better concurrent performance on UFOV3 selective attention compared to prior performance ($\beta = .12, p < .001, f^2 = .02$). They also had poorer concurrent performance on PRT memory compared to prior performance ($\beta = -.08, p = .002, f^2 = .01$). When participants reported one additional wave of pain persistence, they had better concurrent MMSE cognitive status compared to prior performance ($\beta = .22, p < .001, f^2 = .002$).

Covariates Effects.—Time-varying depressive symptoms were not significantly associated with concurrent performance on any task ($ps > .01$, see Tables 2 to 5).

Aim 4. Pain and Rate of Cognitive Change

Baseline Pain.—Participants with baseline pain had accelerated decline in DSST simple processing speed ($\beta = -.12, p < .001, f^2 = .003$, see Figure 3) and MMSE cognitive status ($\beta = -.06, p = .006, A = .004$, see Figure 4). Baseline pain did not significantly impact changes in any other cognitive task ($ps > .01$).

Incident Pain.—After participants reported incident pain, they had decelerated decline in DSST simple processing speed compared to prior performance ($b = .24, p < .001, f^2 = .02$) but accelerated declines in CRT complex processing speed than before ($\beta = -.06, p = .002, f^2 = .01$, shown in Figure 5). Meanwhile, participants experienced more decline in UFOV2 divided attention ($\beta = -.07, p < .001, f^2 = .02$, shown in Figure 6), Word Series reasoning ($\beta = -.05, p < .001, f^2 = .01$, shown in Figure 7), and Letter Series reasoning than before ($\beta = -.06, p < .001, f^2 = .01$, shown in Figure 8). After incident pain, participants also had accelerated decline on PRT memory ($\beta = -.07, p < .001, f^2 = .01$, shown in Figure 9) and MMSE cognitive status compared to prior performance ($\beta = -.06, p = .006, f^2 = .01$, shown in Figure 4). There were no other significant associations between incident pain and cognitive change.

Pain Persistence.—Reporting longer pain persistence was associated with accelerated decline in AVLT memory thereafter $(\beta = -.02, p = .003, f^2 = .004)$. There were no other significant associations between pain persistence and cognitive change $(ps > .01)$.

Covariates Effects.—Time was related to declines in DSST simple processing speed $(\beta = -.35, p < .001, f^2 = .05)$ and increases in Letter Series reasoning $(\beta = .07, p = .004, f^2 = .002)$. That is, over time DSST scores declined while Letter Series scores improved.

Sensitivity Analyses Accounting for Differences in Follow-Up Periods

People with baseline pain ($M = 3.04$, $SD = 1.51$) had fewer waves in the study compared to people reporting incident pain ($M = 3.70$, $SD = 1.31$). However, when accounting for these differences using the number of waves completed as a model covariate, the pattern of aforementioned results did not change.

Discussion

Pain is associated with an increased risk of cognitive impairment and dementia (Bell et al., 2021; Khalid, Sambamoorthi, & Innes, 2020; Tzeng et al., 2018; Whitlock et al., 2017). However, the association between pain and cognitive aging remains unclear. We addressed this gap by examining associations of baseline pain, incident pain, and pain persistence with cognitive function in four aims. We first assessed the frequency and correlates of baseline pain, incident pain, and pain persistence (Aim 1), followed by a cross-sectional assessment of how baseline pain related to baseline cognitive function (Aim 2). We then examined how incident pain and greater pain persistence related to concurrent cognitive function when first reported (Aim 3) and the rate of cognitive decline thereafter (Aim 4). Overall, we found that baseline pain was associated with worse memory at baseline while incident pain and greater pain persistence were associated with accelerated memory decline. Regarding non-memory domains, baseline pain was related to higher initial levels of simple processing speed followed by rapid decline therein, while incident pain was uniquely related to higher initial levels of complex processing speed, divided attention, and reasoning followed by rapid decline therein. Below we summarize our findings by study aim followed by a discussion of clinical and theoretical implications.

In Aim 1, 31% of older adults reported baseline pain, a number lower than that reported in previous samples such as the National Health and Aging Trends Study (53%; Patel et al., 2013). This could be due to the purposeful recruitment of healthy older adults in ACTIVE, or the selection of pain based on moderate-to-severe ratings on the SF-36 rather than presence of any pain in a bodily location. After baseline, incident pain occurred in 42% (n = 289) of the sample – a figure that is nearly identical to the rate of incident pain in the Health and Retirement Study of 43% (7967 of 18439 total older adults; Shi, Hooten, Roberts, & Warner, 2010). Most of the pain reported in our current study had a mean pain persistence of around 2 waves, consistent with pain being commonly persistent in older adults (72% of cases; Larsson et al., 2017). Regarding correlates, unmarried older adults reported baseline pain and pain persistence more often than married older adults, shown in one study before (Larsson et al., 2017). The passage of time was associated with an increased risk of incident pain and longer pain persistence, consistent with pain sensitivity changing with age (Hackett, Naugle, & Naugle, 2020). Even in our mostly healthy sample, greater depressive symptoms were predictive of reporting baseline pain, incident pain, and longer pain persistence in line with previous studies with clinical and non-clinical samples (Magni, Moreschi, Rigatti-Luchini, & Merskey, 1994; Shi et al., 2010). Findings from Aim 1 emphasize the key role of aging and depressive symptoms in elevating the risk of pain in older adults. This is especially important as depression is undertreated in nearly half of this age group (Barry, Abou, Simen, & Gill, 2012),

Baseline pain was associated with worse memory performance in Aim 2, albeit task specific. Older adults with baseline pain had lower baseline performance on the AVLT than those without baseline pain, but groups performed similarly on the HVLT and PRT. It was not expected that we would find many associations between pain and memory performance due to previous studies being rather mixed (Abeare et al., 2010; van der Leeuw et al., 2016; Whitlock et al., 2017). Upon further inspection the AVLT included an interfering word list unlike the other tasks, which may have called upon executive functions requiring higher attentional demands. Findings in Aim 2 highlight the importance of considering task demands when examining how pain relates to specific cognitive domains.

In Aim 3, when older adults first reported incident pain, they had lower concurrent memory on the AVLT task than before. However, unexpectedly, when older adults first reported incident pain, they had better concurrent complex processing speed, divided attention, and reasoning. Older adults with longer pain persistence also showed better concurrent performance in memory and selective attention. These findings counter our hypotheses and previous cross-sectional results in older adults (Karp et al., 2006; Oosterman et al., 2011; van der Leeuw et al., 2018), but are in line with a group of studies also finding a positive association of pain and cognitive function. Oosterman et al. (2009) found that older adults reporting greater pain intensity in assisted living facilities exhibited better executive function. Oosterman et al. (2013) later found that older adults with better executive function were more sensitive to pain on quantitative sensory testing. In a memory clinic, the same research group found a positive association between pain severity and performance on memory and executive function tasks (Madariaga, Overdorp, Claasen, Brazil, & Oosterman, 2021). These results might be explained by cognitive compensation, the recruitment of cognitively-enhancing neural resources to overcome pain-related distraction (Cabeza et al.,

2018). Regions for pain processing and cognitive function overlap, including the prefrontal cortex, hippocampus, and amygdala (i.e., salience detection network; Legrain et al., 2011). Cognitive compensation could lead to more recruitment of these networks to better address cognitive tasks and pain simultaneously. It is also possible that older adults who report incident pain in later life have better integrity of overlapping brain structures for pain and cognitive function, i.e., greater brain reserve, than others, especially compared to older adults who already lived with pain. For example, the positive relationship between pain severity and cognitive function has been shown to be partly explained by white matter integrity (Madariaga et al., 2021). Further study will be needed to discern mechanisms, but our findings align with a handful of studies and emphasize that cross-sectional and concurrent relationships of pain and cognition depend on timing of pain. It appears that associations are more consistent when looking at cognitive decline rather than baseline or concurrent cognitive differences.

In Aim 4, baseline pain was associated with accelerated decline in simple processing speed and cognitive status. This contrasts a previous study in the English Longitudinal Study failing to show associations of baseline pain with simple processing speed, memory, or verbal fluency (Veronese et al., 2018). Discrepancy may be explained by study differences as we assessed cognitive decline over a longer timeframe and classified baseline pain differently. Our study examined cognitive decline up to 10 years while the study in the English Longitudinal Study of Aging only assessed up to four years. A recent review by Aguiar et al. (2020) suggests that assessment of cognitive decline over 4.5 years is needed to detect an association between pain with cognitive decline (e.g., van der Leeuw et al., 2018; Whitlock et al., 2017). We classified baseline pain as reporting moderate-to-severe pain intensity rather than including individuals with mild pain. Moderate-to-severe pain is more aligned with cutoffs used for clinically-significant pain and is associated with cognitive impairment (van der Leeuw et al., 2018). Post-hoc analyses in the English Longitudinal Study of Aging further showed a relationship between severe pain and later memory decline (Veronese et al., 2018).

More hypothesized findings were supported when examining cognitive decline and pain after baseline. Incident pain was related to accelerated decline in complex processing speed, divided attention, paragraph memory recall, reasoning, and cognitive status. This extends earlier studies describing an association of incident pain post- surgery with cognitive decline 3 days to 2 years later (Duggleby & Lander, 1994; Huai et al., 2021). It also builds on another study finding an association of incident pain with four-year decline in cognitive status (Bell, Pope, Downer, Barbara, Crowe, et al., 2021). Lastly, older adults with longer pain persistence had accelerated memory decline. This finding is consistent with studies comparing memory in older adults with and without persistent pain (Karp et al., 2006) and finding a link between persistent pain and memory decline in community-dwelling older adults in the Health and Retirement Study (Bell et al., 2022; Whitaker et al., 2017). Findings from Aim 3 and 4 suggest that early advantages or similarities in cognitive function when pain is first reported are followed by accelerated cognitive decline, possibly as cognitive compensation and brain reserve lose their protective functions (Cabeza et al., 2018).

Our findings may have clinical implications. Older adults typically undergo annual health screenings when accessible. Evaluations that focus on metabolic and cardiovascular health as indicators of major diseases are also relevant to the risk of cognitive impairment, disability, and death (Vogels, Scheltens, Schroeder-Tanka, & Weinstein, 2007). Our findings suggest that pain management and prevention of pain incidence and persistence may help mitigate cognitive decline. Safe regimens include cognitive-behavioral interventions and exercise (de Williams, Fisher, Hearn, & Eccleston, 2020) as well as safe medications like acetaminophen (Haines et al., 2021) among others. Improving pain management is a worthwhile goal as older adults are often unscreened (34%) and undertreated (40%) despite being the most affected by pain in the population (Herr & Titler, 2009). Furthermore, practitioners often use cognitive screeners but should be aware that these measures are less sensitive to identifying changes in cognitive domains related to pain such as tasks requiring problem-solving and reasoning. Comprehensive assessment may not be feasible for screening, but referrals for neuropsychological testing may be beneficial for older adults who have pain and also have subjective reports of cognitive decline. Clinicians should be aware that older adults in pain are more likely to report subjective cognitive decline than older adults without pain (Westoby, Mallen, & Thomas, 2009), representing an important at-risk group.

Our analyses may have important theoretical implications as well. We hypothesized that pain will reduce focus which will worsen cognitive function and accelerate cognitive decline based on the interruptive model of pain. However, as illustrated in Figure 2, we found results that are inconsistent with this general extension of the interruptive model of pain. Namely, pain measures did not consistently relate to worse cognitive function and greater cognitive decline pattern as expected. Instead, baseline pain, incident pain, and pain persistence showed a bump- and-slump pattern, where pain was related to higher levels of some cognitive functions followed by more rapid cognitive decline on some, but not all, cognitive measures. As mentioned, the initial “bump” in cognitive performance could be due to activation of cognitive compensation or better longstanding cognitive reserve, and that the “slump” may occur as compensation fails, or reserve is depleted. This mirrors patterns of associations found for other risk factors for cognitive decline (occupational complexity; Finkel et al., 2009; sex; Levine et al., 2021; education; Singh-Manoux et al., 2011). The Scaffolding Theory of Cognitive Aging may also be suited as it describes this pattern of early compensation and depletion of cognitive reserve, followed by rapid cognitive decline (Reuter-Lorenz et al., 2014) .

Other inconsistent findings were noted. Foremost, associations between pain and cognitive decline were more common when looking at incident pain rather than baseline pain and pain persistence. We theorize that this could be due to the importance of *pain onset*. Incident pain may capture the immediate window of cognitive change where pain exerts its strongest influence, while baseline pain and pain persistence may miss this window because pain originates from young to late midlife. Second, we found that incident pain related to declines in memory, complex processing speed, divided attention, and reasoning while baseline pain related to declines in simple processing speed. Simple processing speed may be most susceptible to decline from pain originating in young to late midlife, while memory and executive function may be more susceptible to decline when pain originates

in older adulthood. Studies have found that processing speed becomes more susceptible to change long before other cognitive domains such as memory and reasoning (Shaie et al., 1996). Lastly, pain persistence accelerated memory decline, suggesting that unmanaged pain is harmful to memory regardless of when onset occurred, consistent with recent findings between pain persistence and memory decline (Bell, Franz, & Kremen, 2021; Whitlock et al., 2017). Further work is needed to develop a model of pain and cognitive aging to account for these complex relationships, considering the roles of pain onset and major aging concepts such as cognitive compensation and reserve. A better theoretical understanding may help reconcile mixed findings in the literature (i.e., Karp et al., 2006; Oosterman et al., 2009, 2013) and help discern who with pain is at higher risk of AD and related dementia (Khalid et al., 2021; Tzeng et al., 2018; Yamada et al., 2019).

Limitations and Strengths

While our study has strengths, there are some limitations worth highlighting. Our sample was largely White (71%) or Black (28%), limiting generalizability to other populations including Latino older adults. This is a particularly important group due to a higher prevalence of severe pain than White older adults (Reyes-Gibby, Aday, Todd, Cleeland, & Anderson, 2007) paired with higher barriers to pain management (Edwards, Moric, Husfeldt, Buvanendran, & Ivankovich, 2005). Latino older adults are also at higher risk of Alzheimer's and related dementias than White older adults (Chen & Zissimopoulos, 2018; Kramarow & Tejada-Vera, 2019). Studies on pain and cognitive decline in Latino communities are hence greatly warranted. Also limiting generalizability, our sample derived from a control group for a clinical trial with rigorous inclusion criteria that might have reduced the inclusion of less healthy adults. Results might vary among older adults selectively sampled to include a greater number of comorbidities such as cardiovascular disease or diabetes who show worse cognitive outcomes than unaffected peers (Vogels, Scheltens, Schroeder-Tanka, & Weinstein, 2007). Lastly, our study had small effect sizes between pain and cognitive decline, although common in risk factors for cognitive decline such as education, cardiovascular disease, depression, and physical activity (f^2s < .02) (Haring et al., 2013; Lopez et al., 2003). Small effects are common in public health and psychological literature but can still have very real-world implications, especially when they involve accumulation over time (Funder & Ozer, 2019). Although we cannot be certain, previous studies suggest that the small but cumulative effects of pain may explain greater rates of cognitive impairment and dementia (Bell, Franz, & Kremen, 2021; Ezzati et al., 2019; Tzeng et al., 2018; van der Leeuw et al., 2018; Whitlock et al., 2017).

This study holds many strengths as well. First, this study included a large sample of community-dwelling older adults, allowing inferences about the pain-cognition relationship to be extended beyond clinical samples. Second, this study was one of the first to look at pain's effect on cognition and pain as they change together in time through multilevel modeling techniques. Lastly, unlike prior work limited to a mental status measure (Kaasalainen et al., 1998) or selective cognitive domains (Karp et al., 2006; Weiner, Rudy, Morrow, Slaboda, & Lieber, 2006), we examined multiple domains of cognition. The inclusion of multiple cognitive domains is critical for determining whether the influence of pain on cognition is more global or whether certain domains are more susceptible to

incident pain. Results from our study suggest pain may negatively affect cognitions ranging from simpler processing speed to more complex attention, memory, and reasoning cognitive domains.

Conclusion

The older adult population will double by 2050, leading to an increase in the number of older adults with pain and cognitive impairment (Gibson & Lussier, 2012; Matthews et al., 2019). Cognitive impairment is hard to reverse, so managing modifiable risk factors like pain may help in protecting healthy cognitive aging. In a mostly healthy sample of older adults, pain contributes to accelerated cognitive decline in a complex manner. Interventions to reduce the new occurrence and persistence of pain in later life will be key to protect healthy cognitive aging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Public Significance Statement:

Pain in later life is related to cognitive decline in older adults and may serve as a key target to curtail poorer cognition in later life.

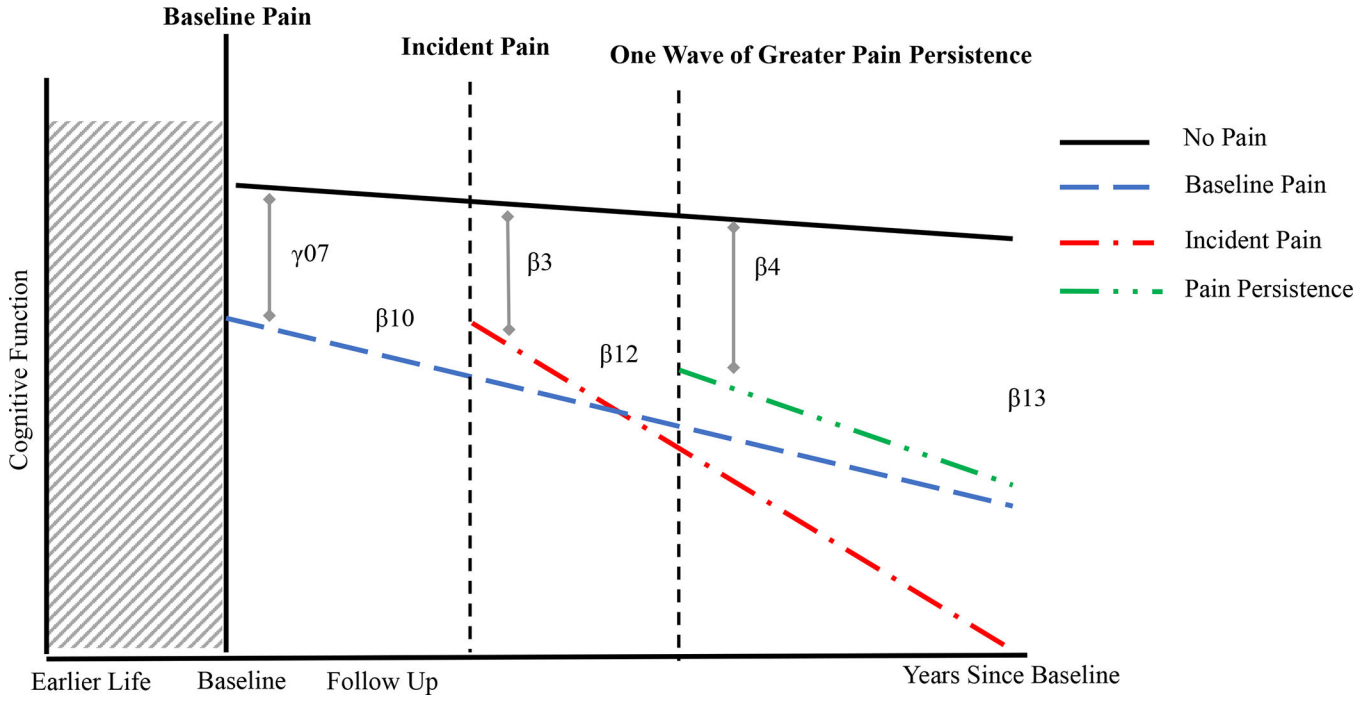

Figure 1.

Illustration of the statistical model. Notes. Baseline pain is a fixed variable coded 0 for not reporting baseline pain and 1 for reporting baseline pain; incident pain is a time-varying variable coded 0 for not reporting incident pain and 1 for reporting incident pain (and 1 consistently thereafter to estimate change in slope). Pain persistence is the running sum of total waves reporting pain. γ07 estimates initial cognitive differences between older adults with and without baseline pain, while β10 estimates differences in the rate of cognitive change. β3 estimates initial cognitive differences between older adults with and without incident pain, while β12 estimates differences in the rate of cognitive change. β4 estimates initial cognitive differences between people experiencing an added wave of pain persistence compared to those who do not, while β13 estimates differences in the rate of cognitive change.

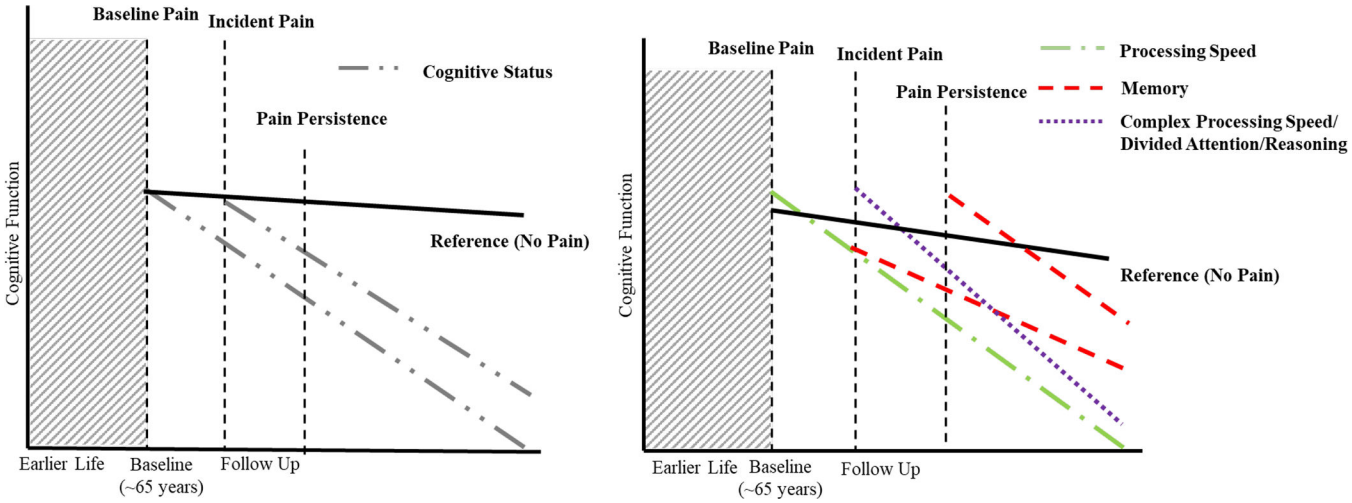

Figure 2.

Summary of study findings.

Notes. Main results:(1) baseline pain and incident pain were related to faster declines in cognitive status (MMSE); (2) baseline pain was related to slower processing speed (3); incident pain was related to worse memory (PRT), divided attention (UFOV2), and reasoning (Word Series and Letter Series); (4) pain persistence was related to accelerated memory decline (AVLT); and (5) except for mental status and memory measures, people with baseline pain and incident pain showed initial cognitive function in domains they eventually declined faster in compared to people with no pain, possibly due to activation of cognitive compensation or longstanding differences in cognitive reserve. Gray diagonal lines: Baseline pain may have involved pain from earlier life, which may have influenced our findings. AVLT = Auditory Verbal Learning Task; PRT = Rivermead Paragraph Recall Task; MMSE = Mini Mental Status Examination.

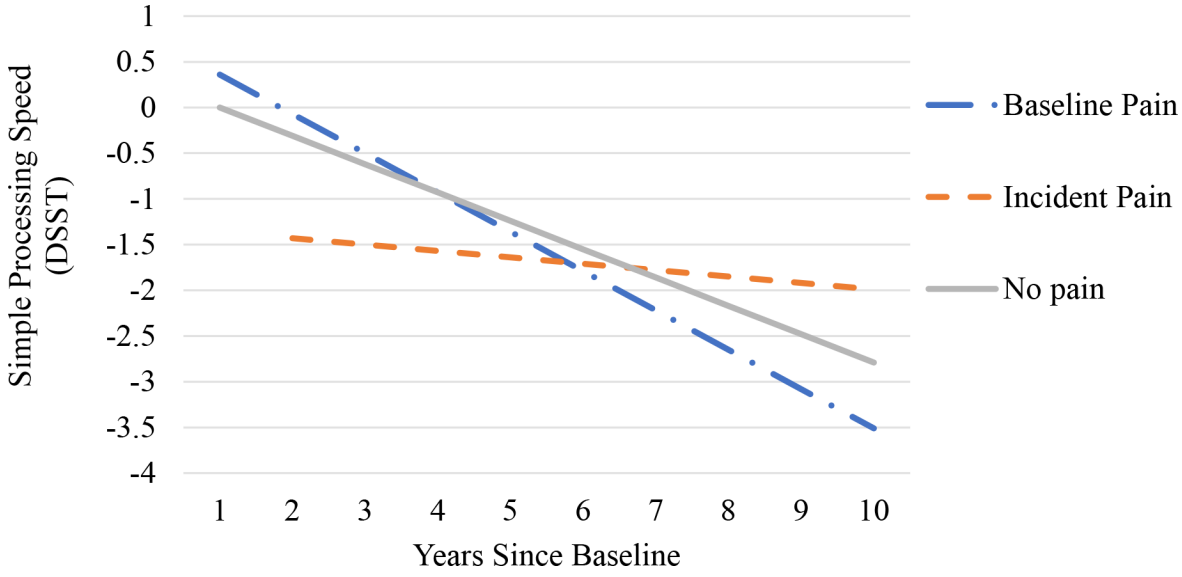

Figure 3.
Differences in simple processing speed in people with baseline pain, incident pain, and no pain. Note. DSST = Digit Symbol Substitution Task.

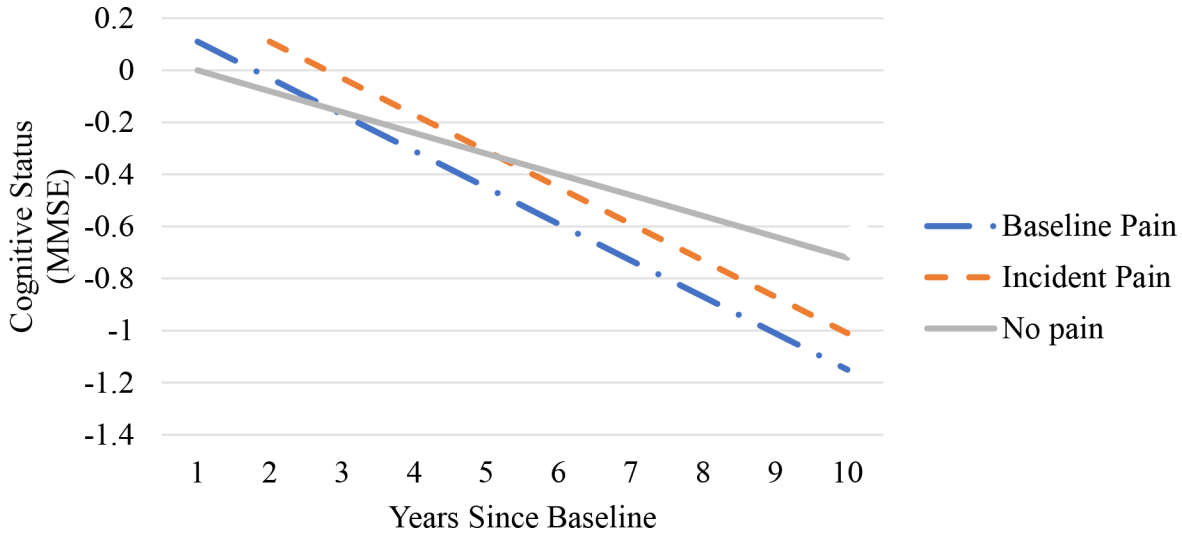

Figure 4.

Differences in cognitive status in people with baseline pain, incident pain, and no pain. Note. MMSE = Mini-Mental Status Examination.

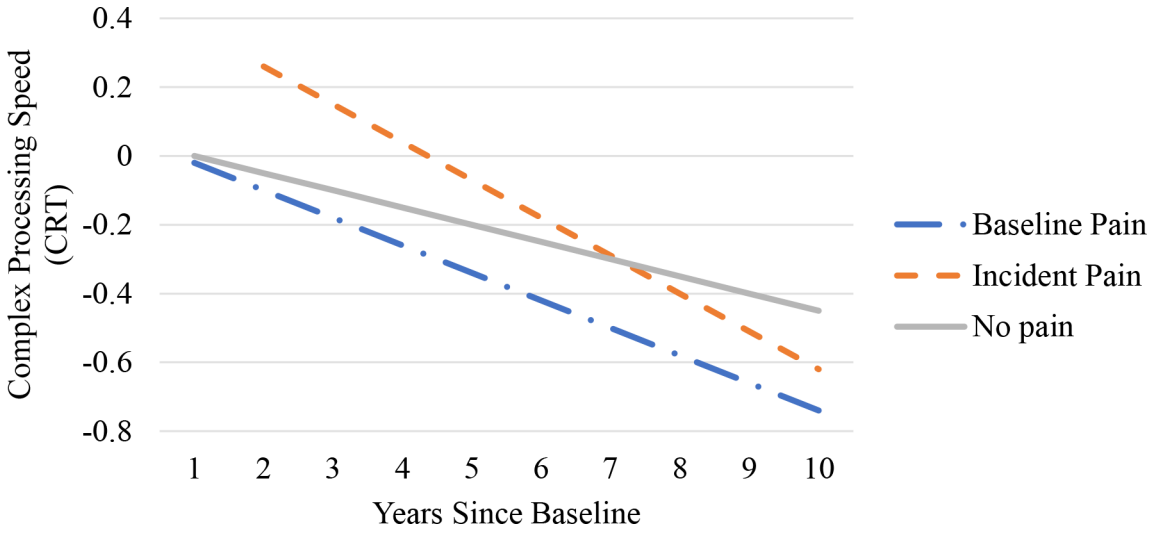

Figure 5.
Differences in complex processing speed in people with baseline pain, incident pain, and no pain. Note. CRT = Complex Reaction Time.

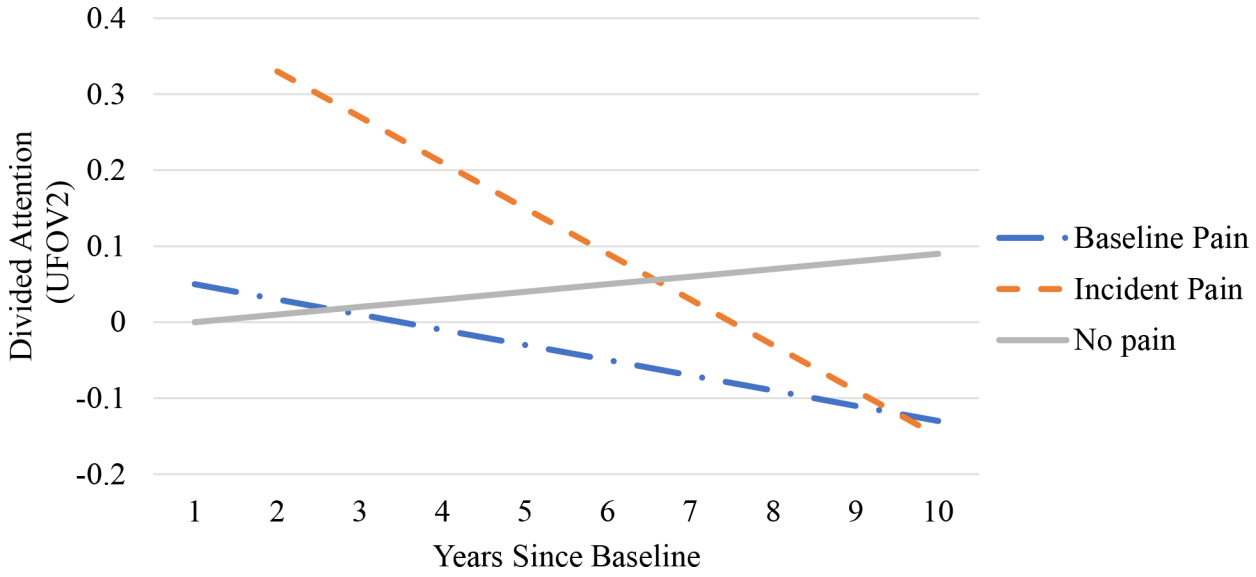

Figure 6.

Differences in divided attention in people with baseline pain, incident pain, and no pain.

Note. UFOV2 = Useful Field of View Subtest 2.

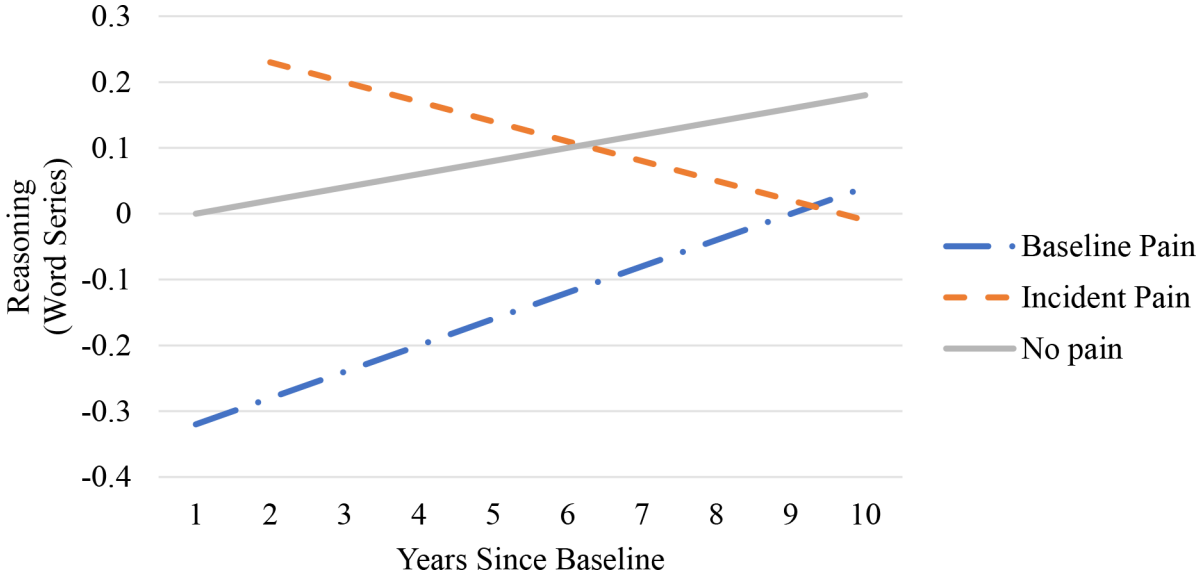

Figure 7.
Differences in reasoning on the Word Series task in people with baseline pain, incident pain, and no pain.

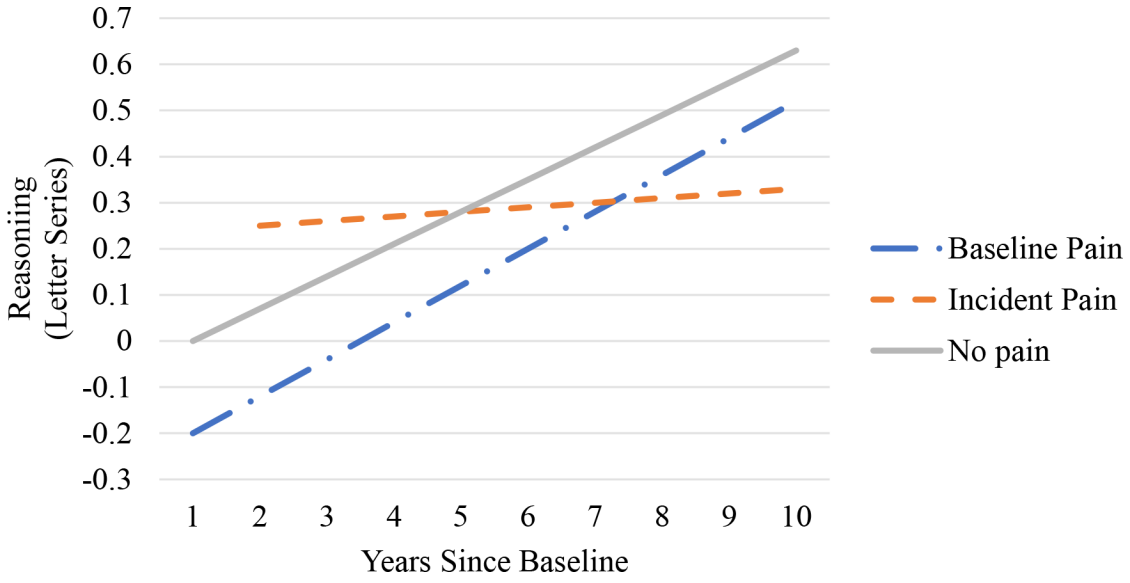

Figure 8.
Differences in reasoning on the Letter Series task in people with baseline pain, incident pain, and no pain.

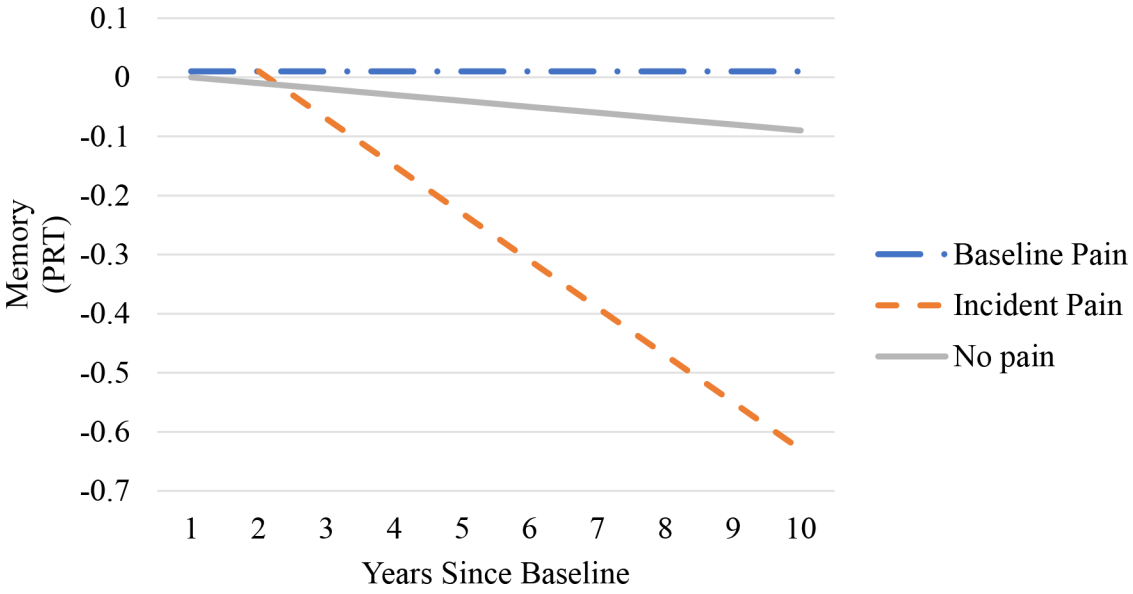

Figure 9.
Differences in memory in people with baseline pain, incident pain, and no pain. Note. PRT = Rivermead Paragraph Recall Task.

Table 1.

Descriptives and intercorrelations between study variables (n = 688).

	Sample Characteristics				*Baseline Pain*		*Age*		Education		Race		Women Gender		Marital Status	
	%	*n*	*M*	*SD*	*r* *	*p*	*r* *	*p*	*r* *	*p*	*r* *	*p*	*r* *	*p*	*r* *	*p*
Baseline Pain	31.0%	210	26.03	21.22	--	--	.03	.38	−.14	<.001	.03	.376	−.11	.004	−.14	<.001
Demographics																
Age (years)			73.96	5.99	.03	.38			−.09	.015	−.05	.209	.04	.293	−.22	<.001
Education (years)			13.39	2.70	−.14	<.001	−.09	.015			−.11	.003	.21	<.001	.21	<.001
Race					.03	.376	−.05	.209	−.11	.003			−.11	.003	−.13	.001
White (ref)	71.1	489														
Non-White	28.9	199														
Gender					−.11	.004	.04	.293	.21	<.001	−.11	.003			.34	<.001
Men	26.3%	181														
Women (ref)	73.7%	507														
Marital Status					−.14	<.001	−.22	<.001	.21	<.001	−.13	.001	.34	<.001		
Married (ref)	37.5%	258														
Widowed/Single	52.5%	430														
CESD (total score)			5.06	4.87	.29	<.001	.09	.024	−.27	<.001	.07	.085	−.15	<.001	−.13	.001
Cognitive Status																
MMSE (total score)			27.31	1.97	−.05	.18	−.17	<.001	.28	<.001	−.21	<.001	.05	.158	.14	<.001
Processing Speed																
DSST (# correct)			39.82	11.45	−.16	<.001	−.32	<.001	.26	<.001	−.25	<.001	−.06	.147	.15	<.001
CRT (s)			2.10	1.15	.11	.004	−.37	<.001	−.37	<.001	.25	<.001	−.12	.003	−.2	<.001
Attention																
UFOV®2 (ms)			138.99	128.42	−.07	.055	−.39	<.001	−.39	<.001	.15	<.001	−.06	.113	−.21	<.001
UFOV®3 (ms)			326.07	134.29	−.07	.082	−.4	<.001	−.4	<.001	.12	.002	−.02	.594	−.18	<.001
UFOV®4 (ms)					−.03	.48	−.31	<.001	−.31	<.001	.09	.014	.02	.702	−.09	.015
Memory																
HVLT (# correct)			25.91	5.64	−.11	.003	−.35	<.001	.25	<.001	−.15	<.001	−.23	<.001	.12	.001
RAVLT (# correct)			48.05	1.90	−.06	.11	−.35	<.001	.2	<.001	−.09	.02	−.27	<.001	.07	.051

	Sample Characteristics				Baseline Pain		Age		Education		Race		Women Gender		Marital Status	
	%	n	M	SD	r *	p	r *	p	r *	p	r *	p	r *	p	r *	p
PRT (# correct)			6.21	2.68	−.04	.351	−.24	<.001	.31	<.001	−.26	<.001	.01	.719	.22	<.001
Fluid intelligence																
Letter Sets (# correct)			5.64	2.90	−.11	.003	−.29	<.001	.4	<.001	−.31	<.001	.05	.169	.18	<.001
Word Series (# correct)			9.30	4.81	−.11	.003	−.31	<.001	.37	<.001	−.29	<.001	.06	.132	.19	<.001

Note. CESD = Center for Epidemiologic Studies Depression Scale; CRT = Complex Reaction Time; DSST = Digit Symbol Substitution Task; HVLT = Hopkins Verbal Learning Task; MMSE = Mini-Mental Status Exam, PRT = Rivermead Paragraph Recall Task Task, RAVLT = Rey Auditory Verbal learning Task ; UFOV = Useful Field of View.

*Kendall-Tau point-biserial correlation used for categorical variables; Spearman's rho correlation used for continuous variables.

Table 2.

Longitudinal Associations of Pain and Covariates with Processing Speed.

	DSST			CRT		
Baseline Cognitive Function	**β**	***p***	f^2	**β**	***p***	f^2
Baseline Age, γ01	**−.02**	**<.001**	.01	**−.06**	**<.001**	.03
Race (White), γ02	.09	.078	.001	**.31**	**<.001**	.01
Gender (Woman), γ03	−.02	.808	<.001	−.01	.880	<.001
Education (Years), γ04	.01	.145	<.001	.02	.142	<.001
Marital Status (Married/Partnered), γ05	−.04	.377	.001	−.02	.853	<.001
Baseline Depressive Symptoms, γ06	.01	.219	<.001	**−.02**	.003	.01
Baseline Pain (Yes), γ07	**.36**	**<.001**	.01	−.02	.306	<.001
Concurrent Cognitive Function						
Time-varying Depressive Symptoms, β2	<.001	.919	<.001	−.01	.435	.001
Incident Pain, β3	**−1.43**	**<.001**	.05	**.26**	**.009**	.01
Pain persistence, β4	.001	.989	<.001	.10	.091	.003
Rate of Cognitive Decline						
Time (Years After Baseline), β1	**−.31**	**<.001**	.05	−.05	.189	.004
Race (White)*Time, β5	.02	.147	.002	−.01	.569	<.001
Gender (Woman)*Time, β6	**−.06**	**<.001**	.01	.01	.360	<.001
Education (Years)*Time, β7	**.01**	**.006**	.01	<.001	.835	<.001
Marital Status (Married/Partnered)*Time, β8	**.03**	**.008**	.01	.01	.347	.003
Baseline Depressive Symptoms*Time, β9	**−.01**	**.005**	.002	<.001	.631	<.001
Baseline Pain (Yes)*Time, β10	**−.12**	**<.001**	.003	−.03	.262	.002
Time-varying Depressive Symptoms*Time, β11	.001	.386	<.001	−.001	.363	.002
Incident Pain*Time, β12	**.24**	**<.001**	.02	**−.06**	**.002**	.01
Pain Persistence*Time, β13	.01	.118	.002	.002	.811	.004
Random Effects						
Residual, σ^2_e	.06			.45		
Intercept, σ^2_μ	.07			.41		
Time, σ^2_{Time}	.03			.01		

	DSST			CRT		
Baseline Cognitive Function	**β**	***p***	***f*** ^{2}	**β**	***p***	***f*** ^{2}
Intraclass Correlation	.44			.48		
Marginal r^2	.22			.17		

Note. CRT = Complex Reaction Time, DSST = Digit Symbol Substitution Task. Dependent variables of the multilevel models are the cognitive tasks listed in the columns (representing a separate model) and predictors are listed in the rows (representing model predictors). Higher scores on the cognitive tasks indicate better cognitive function. Intraclass correlation is the correlation between observations within a person. Bolded values in the second to last columns represent statistically significant values ($ps < .01$).

Table 3.

Longitudinal Associations of Pain and Covariates with Divided and Selective Attention.

	UFOV2 – Divided Attention			UFOV3-Selective Attention			UFOV4-Selective Attention		
Baseline Cognitive Function	**β**	***p***	f^2	**β**	***p***	f^2	**β**	***p***	f^2
Baseline Age, γ01	**−.07**	**<.001**	.04	**−.08**	**<.001**	.04	**−.05**	**<.001**	.002
Race (White), γ02	**.27**	**<.001**	.01	**.26**	**<.001**	.001	**.26**	**.002**	.002
Gender (Woman), γ03	−.15	.078	.003	−.09	.281	.001	−.07	.410	<.001
Education (Years), γ04	**.06**	**<.001**	.002	**.04**	.002	.001	**.04**	**.006**	.01
Marital Status (Married/Partnered), γ05	.15	**<.001**	.001	.14	.079	.001	−.01	.911	<.001
Baseline Depressive Symptoms, γ06	−.01	.402	.001	−.02	.121	.002	−.01	.502	<.001
Baseline Pain (Yes), γ07	.05	.609	<.001	−.23	.013	.01	−.23	.032	.003
Concurrent Cognitive Function									
Time-varying Depressive Symptoms, β2	−.01	.239	<.001	.001	.848	<.001	−.01	.473	.01
Incident Pain, β3	**.33**	**<.001**	.02	.10	.222	<.001	.02	.872	.001
Pain Persistence, β4	−.10	.050	.004	**.12**	**<.001**	.02	.14	.016	.01
Rate of Cognitive Change									
Time (Years After Baseline), β1	.01	.876	.001	.01	.877	<.001	−.04	.279	.002
Race (White)*Time, β5	.02	.101	.003	−.004	.721	<.001	−.01	.394	.001
Gender (Woman)*Time, β6	.04	.003	.003	.03	.052	.002	.02	.318	.002
Education (Years)*Time, β7	−.002	.214	.003	−.002	.250	<.001	−.002	.406	.002
Marital Status (Married/Partnered)*Time, β8	−.02	.131	<.001	−.01	.507	<.001	.01	.704	<.001
Baseline Depressive Symptoms*Time, β9	−.002	.255	.002	−.001	.552	.001	<.001	.855	<.001
Baseline Pain (Yes)*Time, β10	−.03	.142	.001	−.01	.598	.002	−.01	.707	<.001
Time-varying Depressive Symptoms*Time, β11	−.002	.206	.002	−.001	.501	<.001	<.001	.543	<.001
Incident Pain*Time, β12	**−.07**	**<.001**	.02	−.03	.054	.001	−.02	.343	.002
Pain Persistence*Time, β13	.002	.823	<.001	−.02	.011	.001	−.01	.017	.001
Random Effects									
Residual, σ^2_e	.30			.27			.51		
Intercept, σ^2_μ	.42			.48			.39		
Time, σ^2_{Time}	.02			.01			.02		

	UFOV2 – Divided Attention			UFOV3-Selective Attention			UFOV4-Selective Attention		
Baseline Cognitive Function	**β**	***p***	**f^2**	**β**	***p***	**f^2**	**β**	***p***	**f^2**
Intraclass Correlation	.57			.63			.42		
Marginal r^2	.23			.23			.11		

Note. UFOV = Useful Field of View. Dependent variables of the multilevel models are the cognitive tasks listed in the columns (representing a separate model) and predictors are listed in the rows (representing model predictors). Higher scores on the cognitive tasks indicate better cognitive function. Intraclass correlation is the correlation between observations within a person. Bolded values in the second to last columns represent statistically significant values ($ps < .01$).

Table 4.

Longitudinal Associations of Pain and Covariates with Memory.

	HVLT			AVLT			PRT		
Baseline Cognitive Function	**β**	***p***	***f*** ^{2}	**β**	***p***	***f*** ^{2}	**β**	***p***	***f*** ^{2}
Baseline Age, γ01	**−.06**	**<.001**	.03	**−.07**	**<.001**	.05	**−.05**	**<.001**	.003
Race (White), γ02	**.37**	**<.001**	.01	.37	.031	.004	.52	.741	.02
Gender (Woman), γ03	**−.61**	**<.001**	.02	**−.73**	**<.001**	.01	**−.18**	**<.001**	.003
Education (Years), γ04	**.06**	**<.001**	.001	**.07**	**<.001**	.002	.10	.023	.02
Marital Status (Married/Partnered), γ05	.05	.478	.001	.02	**<.001**	<.001	**.15**	**<.001**	.01
Baseline Depressive Symptoms, γ06	**−.03**	**.002**	.01	**−.02**	.826	**.01**	−.02	.012	.01
Baseline Pain (Yes), γ07	−.08	.335	<.001	**−.29**	**.001**	.004	.01	.050	.001
Concurrent Cognitive Function									
Time-varying Depressive Symptoms, β2	−.01	.142	.003	−.01	.336	.003	−.01	.661	<.001
Incident Pain, β3	.04	.624	<.001	**−.27**	**.002**	.004	.01	.953	.004
Pain persistence, β4	.05	.352	<.001	**.22**	**<.001**	.002	**−.08**	**.002**	.01
Rate of Cognitive Decline									
Time (Years After Baseline), β1	−.06	.068	.003	−.07	.073	.002	−.01	.277	.01
Race (White)*Time, β5	−.01	.237	.002	−.02	.145	.01	.00	.945	.01
Gender (Woman)*Time, β6	−.01	.270	.001	.01	.404	.001	.03	.028	.002
Education (Years)*Time, β7	<.01	.808	<.001	.00	.773	<.001	.00	.414	<.001
Marital Status (Married/Partnered)*Time, β8	.02	.055	<.001	.02	.173	.002	−.01	.367	.002
Baseline Depressive Symptoms*Time, β9	<.01	.831	<.001	.00	.548	.002	.00	.896	<.001
Baseline Pain (Yes)*Time, β10	−.03	.083	.05	.03	.076	.002	.01	.612	<.001
Time-varying Depressive Symptoms*Time, β11	<.01	.215	.002	.00	.446	.001	.00	.844	<.001
Incident Pain*Time, β12	.01	.437	.001	.02	.189	<.001	**−.07**	**<.001**	.01
Pain Persistence*Time, β13	.003	.658	<.001	**−.02**	**.003**	.004	.04	.280	<.001
Random Effects									
Residual, σ^2_e	.30			.26			.36		
Intercept, σ^2_μ	.36			.42			.31		
Time, σ^2_{Time}	.05			.05			.04		

Psychol Aging. Author manuscript; available in PMC 2023 September 01.

	HVLT			AVLT			PRT		
Baseline Cognitive Function	**β**	***p***	***f*²**	**β**	***p***	***f*²**	**β**	***p***	***f*²**
Intraclass Correlation	.51			.58			.44		
Marginal r^2	.29			.29			.26		

Note. AVLT = Auditory Verbal Learning Task; HVLT = Hopkins Verbal Learning Task; PRT = Rivermead Paragraph Recall Task. Dependent variables of the multilevel models are the cognitive tasks listed in the columns (representing a separate model) and predictors are listed in the rows (representing model predictors). Higher scores on the cognitive tasks indicate better cognitive function. Intraclass correlation is the correlation between observations within a person. Bolded values in the second to last columns represent statistically significant values ($ps < .01$).

Table 5.

Longitudinal Associations of Pain and Covariates with Reasoning and Cognitive Status.

	Word Series			Letter Series			MMSE		
Baseline Cognitive Function	**β**	***p***	***f*²**	**β**	***p***	***f*²**	**β**	***p***	***f*²**
Baseline Age, γ01	**−.06**	**<.001**	.03	**−.06**	**<.001**	.02	**−.03**	**<.001**	.01
Race (White), γ02	**.61**	**<.001**	.01	**.64**	**<.001**	.01	.20	.014	.01
Gender (Woman), γ03	−.20	.016	<.001	**−.26**	**.001**	.001	−.01	.901	<.001
Education (Years), γ04	**.11**	**<.001**	.002	**.12**	**<.001**	.01	**.06**	**<.001**	.01
Marital Status (Married/Partnered), γ05	.003	.942	.002	−.04	.617	.001	.01	.863	<.001
Baseline Depressive Symptoms, γ06	**−.03**	**<.001**	.01	**−.03**	<.001	.01	**−.02**	.026	.01
Baseline Pain (Yes), γ07	−.32	.022	.002	−.20	.016	.002	.11	.332	<.001
Concurrent Cognitive Function									
Time-varying Depressive Symptoms, β2	−.01	.036	<.001	.004	.496	.002	−.01	.360	.003
Incident Pain, β3	**.23**	**<.001**	.01	**.25**	**<.001**	.01	.11	.415	<.001
Pain persistence, β4	−.08	.025	.01	−.08	.038	.004	−.02	.800	<.001
Rate of Cognitive Change									
Time (Years After Baseline), β1	.02	.378	<.001	**.07**	**.004**	.002	−.08	.026	.004
Race (White)*Time, β5	.004	.638	<.001	−.02	.253	.001	**.04**	**.002**	.01
Gender (Woman)*Time, β6	.01	.520	<.001	.01	.174	<.001	−.01	.437	.002
Education (Years)*Time, β7	.003	.080	<.001	**.01**	**.002**	.01	.002	.314	.001
Marital Status (Married/Partnered)*Time, β8	.01	.284	<.001	.01	.216	<.001	.01	.676	.001
Baseline Depressive Symptoms*Time, β9	.002	.837	<.001	.001	.559	<.001	.001	.513	.001
Baseline Pain (Yes)*Time, β10	.02	.179	.003	.01	.457	.002	**−.06**	**.006**	.004
Time-varying Depressive Symptoms*Time, β11	−.001	.114	<.001	.002	.081	.001	.001	.640	.001
Incident Pain*Time, β12	**−.05**	**<.001**	.01	**−.06**	**<.001**	.01	**−.06**	**.006**	.01
Pain persistence*Time, β13	.01	.360	.001	.001	.818	<.001	.02	.043	.01
Random Effects									
Residual, σ^2_e	.48			.16			.40		
Intercept, σ^2_μ	.16			.48			.37		
Time, σ^2_{Time}	.01			.02			.03		

	Word Series			Letter Series			MMSE		
Baseline Cognitive Function	**β**	***p***	***f*²**	**β**	***p***	***f*²**	**β**	***p***	***f*²**
Intraclass Correlation	.27			.73			.46		
Marginal r^2	.34			.17			.14		

Note. MMSE = Mini-Mental Status Examination. Dependent variables of the multilevel linear mixed models are listed in the columns (representing a separate model) and predictors are listed in the rows (representing estimates for each model). Intraclass correlation is the correlation between observations within a person. Bolded values in the second to last columns represent statistically significant values (*p*s < .01).