PNAS RESEARCH ARTICLE | PSYCHOLOGICAL AND COGNITIVE SCIENCES

Elevated dementia risk, cognitive decline, and hippocampal atrophy in multisite chronic pain

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Edited by Steven Small, The University of Texas at Dallas; received September 8, 2022; accepted January 18, 2023 by Editorial Board Member Michael S. Gazzaniga

Numerous studies have investigated the impacts of common types of chronic pain (CP) on patients' cognitive function and observed that CP was associated with later dementia. More recently, there is a growing recognition that CP conditions frequently coexist at multiple body sites and may bring more burdens on patients' overall health. However, whether and how multisite CP (MCP) contributes to an increased risk of dementia, compared to single-site CP (SCP) and pain-free (PF), is largely unclear. In the current study, utilizing the UK Biobank cohort, we first investigated dementia risk in individuals (n = 354,943) with different numbers of coexisting CP sites using Cox proportional hazards regression models. We then applied generalized additive models to investigate whether MCP leads to excessive deterioration of participants' (n = 19,116) cognition and brain structure. We found that individuals with MCP were associated with significantly higher dementia risk, broader and faster cognitive impairment, and greater hippocampal atrophy than both PF individuals and those with SCP. Moreover, the detrimental effects of MCP on dementia risk and hippocampal volume aggravated along with the number of coexisting CP sites. Mediation analyses further revealed that the decline of fluid intelligence in MCP individuals was partially mediated by hippocampal atrophy. Our results suggested that cognitive decline and hippocampal atrophy interact biologically and may underlie the increased risk of dementia associated with MCP.

multisite chronic pain | dementia | cognitive function | hippocampus | UK Biobank

Chronic pain (CP) is one of the leading causes of disability affecting 30% of people worldwide, and its prevalence increases strongly with age (1, 2). In addition to causing physical and psychological suffering, CP has a major effect on cognitive functions, encompassing processing and psychomotor speed, memory and learning, attention, and executive functions (3–5). Moreover, several recent studies highlighted a higher slope of age-related cognitive decline in CP individuals than in the normal aging population (6–8). Since the impairment of cognitive functions is an essential feature of dementia at diagnosis (9, 10), and the pathology of dementia is often accompanied by accelerated cognitive declination (11, 12), dementia incidence was assumed to be higher in patients with CP in comparison to pain-free (PF) individuals (13). Indeed, recent longitudinal studies have confirmed the association between CP and later dementia, showing that the CP elderly experienced greater memory loss and an increased risk of cognitive impairment (8, 14, 15).

As numerous studies have investigated the impacts of common types of CP on cognitive functions and brain health, there is a growing recognition that different CP conditions frequently coexist and may share common neurobiological vulnerabilities (16, 17), leading to multisite CP (MCP). At the population level, roughly half of the CP individuals report CP at multiple body sites (18, 19). Even though a considerably high prevalence rate was observed, the overlapping nature of pain conditions was frequently neglected in previous studies. Multiple lines of evidence have suggested that MCP relates to extra burdens on psychiatric, autoimmune, and anthropometric traits (20); risk of coronary artery disease (21); axonogenesis in the hippocampal limbic system (18); and quality of life (22), most of which were key factors that aggravate cognitive impairment and dementia progression (23–32). Nevertheless, whether and to what extent MCP is associated with dementia risk and cognitive decline, compared to both PF and single-site CP (SCP), is unknown.

Although a host of biological associations with dementia in CP patients have been identified, such as altered brain function and structure (33–35), inflammation (36, 37), and genetic risk factors (18, 20, 38), there is no consensus on the neural mechanisms underlying the link between CP and dementia (13). As a key structure for learning and memory (39, 40), the hippocampal volume, which was sensitive to the onset of dementia (27, 41–43), was frequently observed to be atrophied in CP patients (34, 44, 45). These findings indicate a possible role of the hippocampus in the development of dementia in CP patients. A recent genome-wide study has linked MCP and hippocampal abnormality

Significance

Nearly half of chronic pain patients report pain at multiple anatomical locations, referred to as multisite chronic pain (MCP). Whether individuals with MCP suffered from aggravated neurocognitive abnormalities, compared to individuals with single-site chronic pain (SCP) and those with no pain, remains unknown. Utilizing longitudinal (n = 354,943) and cross-sectional data (n = 19,116) from the UK Biobank, we found that individuals with MCP had increased dementia risk, accelerated cognitive decline, and decreased hippocampal volume compared to pain-free controls and individuals with SCP. Our findings highlight the excessive burdens of MCP on patients' cognition and brain and suggest a need to account for the overlapping nature of pain conditions in future studies.

Author contributions: Y.T. designed research; W.Z. and Y.T. performed research; W.Z., L.Z., and Y.T. analyzed data; and W.Z., X.C., X.L., and Y.T. wrote the paper.

The authors declare no competing interest.

This article is a PNAS Direct Submission. S.S. is a guest editor invited by the Editorial Board.

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This article contains supporting information online at https://www.pnas.org/lookup/suppl/doi:10.1073/pnas.2215192120/-/DCSupplemental.

Published February 21, 2023.

with the DCC netrin 1 receptor (DCC) gene (18), which was responsible for axonogenesis and was expressed mainly in the hippocampus (18). However, whether the hippocampal abnormality can be observed and serve as a key neurobiological mechanism underlying cognitive decline in MCP are still unclear.

In the present study, we sought to characterize the detrimental effects of MCP on human cognition and brain structure with cross-sectional and longitudinal datasets from the UK Biobank. Specifically, we first investigated whether the risk of dementia was significantly higher in MCP than in both PF and SCP (n = 354,943). With Cox proportional hazards regression models, which were widely used in time-to-event analyses (46, 47), we estimated the hazard ratios (HRs) and 95% CIs to summarize the effect of MCP on dementia incidence during the follow-up. Second, we investigated whether MCP exerted excessive burdens on participants' (n = 19,116) cognitive performances at both intercepts and aging trajectories. We took advantage of generalized additive models (GAMs) (48), which were frequently applied in large-scale studies studying development and aging trajectories (49), to detect performance differences while comparing nonlinear relationships between cognitive performances and age in different CP conditions. Third, GAMs were also applied to check the intercepts and aging trajectories abnormality of bilateral total hippocampal volume in MCP. We subsequently quantified whether atrophy of the hippocampus intensified along with the number of coexisting CP sites and equivalent the effect to normal aging. Last, we performed mediation analyses to associate cognitive decline with hippocampal atrophy in MCP.

Results

Study Sample. To evaluate the risk of dementia among individuals with or without CP, 354,943 individuals (age range = 39 to 73 y) from the UK Biobank baseline assessment who fulfilled the inclusion criteria (*SI Appendix*, Fig. S1) were included in the data analysis, consisting of 188,746 PF controls, 76,206 with SCP (i.e., individuals with CP at single body site), and 89,991 with MCP. During a mean follow-up of 11.8 (SD = 1.7) y, 4,222 (PF, n = 1,842; SCP, n = 948; MCP, n = 1,432) individuals developed dementia.

A subset of participants (n = 44,172) from the baseline assessment completed the brain MRI data collection during the first imaging assessment. To further explore the influence of MCP on cognitive functions and hippocampal volume, we screened 26,407 middle-aged and older adults (age range = 45 to 82 y) with cognitive assessments and MRI scans that satisfied our inclusion criteria (*SI Appendix*, Fig. S1). Following a matching process (i.e., matching the age and gender of each group; details in *SI Appendix*), a total of 19,116 individuals, consisting of 9,558 PF controls, 5,597 with SCP, and 3,961 with MCP, were included.

The summary of the CP overlapping condition is depicted in *SI Appendix*, Fig. S2, and the characteristics of the included samples are shown in *SI Appendix*, Tables S1 and S2. In comparison with participants from the other two groups, participants with MCP were more likely to be female; were non-White; consumed more aspirin, paracetamol, and ibuprofen; were current smokers; have lower socioeconomic status (i.e., higher Townsend deprivation index), have lower educational attainment, have higher body mass index (BMI), have more disease histories (i.e., diabetes, cancer, vascular or heart problems), and sought treatment for nervousness, anxiety, tension, or depression.

Multisite CP Was Associated with an Increased Risk of Dementia. To investigate whether MCP elevated the risk of dementia, Cox proportional hazards regression models were generated. The HRs calculated from the Cox model represented the relative dementia risk of CP conditions compared to PF. Proportional hazards assumptions of the Cox models were checked with the Schoenfeld residuals (50) method (see *Materials and Methods* for details). No violation was observed after the false discovery rate (FDR) correction. Models were first established for three categories of CP conditions (i.e., PF, SCP, and MCP) with minimal adjustment for age, gender, ethnicity, and medications. Compared to PF, the risks of dementia (i.e., HRs) for SCP and MCP were 1.19-fold and 1.55-fold higher, respectively (SCP, HR = 1.19, 95% CI, 1.10 to 1.29; MCP, HR = 1.55, 95% CI, 1.44 to 1.67). When additionally adjusted for full potential confounders, including Townsend deprivation index, educational attainment, BMI, smoking status, alcoholic drinking status, history of cancer, history of diabetes, history of vascular or heart problems (angina, hypertension, heart attack, and stroke), and ever seen a doctor (i.e., general practitioner) for nervousness, anxiety, tension, or depression, the risks of dementia for SCP and MCP were 1.15-fold and 1.36-fold higher than PF, respectively (SCP, HR = 1.15, 95% CI, 1.06 to 1.24; MCP, HR = 1.36, 95% CI, 1.26 to 1.47; Fig. 1*A*). Notably, MCP demonstrated a significant higher dementia risk than SCP (basic adjusted model, HR = 1.30, 95%CI, 1.20 to 1.42; full adjusted model, HR = 1.19, 95% CI, 1.09 to 1.30).

To further explore whether the dementia risk increased along with the number of coexisting CP sites, six-category (i.e., PF, SCP, and CP at 2, 3, 4, and 5 or more body sites) models were then established with PF as the reference group. The risk of dementia was higher in individuals with more coexisting CP sites, regardless of whether full covariates were adjusted (Fig. 1*B*). Specifically, the dementia risks for CP at 1 to 5 or more body sites were 1.20-, 1.41-, 1.68-, 1.93-, and 2.12-fold higher than PF, respectively (single site, HR = 1.20, 95% CI, 1.10 to 1.29; two sites, HR = 1.41, 95% CI, 1.29 to 1.54; three sites, HR = 1.68, 95% CI, 1.50 to 1.87; four sites, HR = 1.93, 95% CI, 1.66 to 2.25; five sites, HR = 2.12, 95% CI, 1.67 to 2.70); while the dementia risks were 1.15-, 1.28-, 1.44-, 1.56-, and 1.59-fold higher than PF (single site, HR = 1.15, 95% CI, 1.06 to 1.24; two sites, HR = 1.28, 95% CI, 1.18 to 1.40; three sites, HR = 1.44, 95% CI, 1.29 to 1.61; four sites, HR = 1.56, 95% CI, 1.34 to 1.82; five sites, HR = 1.59, 95% CI, 1.25 to 2.03) after adjusting for full covariates. These significant results survived after the FDR correction for the *P* values.

Multisite CP Was Associated with Accelerated Cognitive Decline. To check whether MCP could bring excessive burdens on participants' cognition, GAM-based regression was used to model the intercepts and aging trajectories of participants' performance on cognitive tests. Age, gender, medications, Townsend deprivation index, BMI, height, ethnicity, smoking status, alcoholic drinking status, and the first ten genetic principal components (i.e., to control for the genetic population structure; see *Materials and Methods*) were included in the covariate set. For the intercepts, GAMs detected significant main effects of groups (i.e., PF, SCP, and MCP) for most of the cognitive tests (Fig. 2*A*). Post-hoc tests revealed that compared with the other two groups, the MCP group performed worse on 7 out of 11 cognitive tests (i.e., fluid intelligence, matrix pattern completion, numeric memory, paired associate learning, prospective memory, symbol digit substitution, and trail making-B [TMT-b]), after FDR correction (Fig. 2*A*). In contrast, SCP only showed worse performance than PF controls in prospective memory test (t = 2.489, P = 0.013) and TMT-b (t = −2.293, P = 0.022). Full statistical results can be found in *SI Appendix*, Table S3.

The aging trajectories of cognitive functions for participants in different groups are depicted in Fig. 2*B*. It is noteworthy that

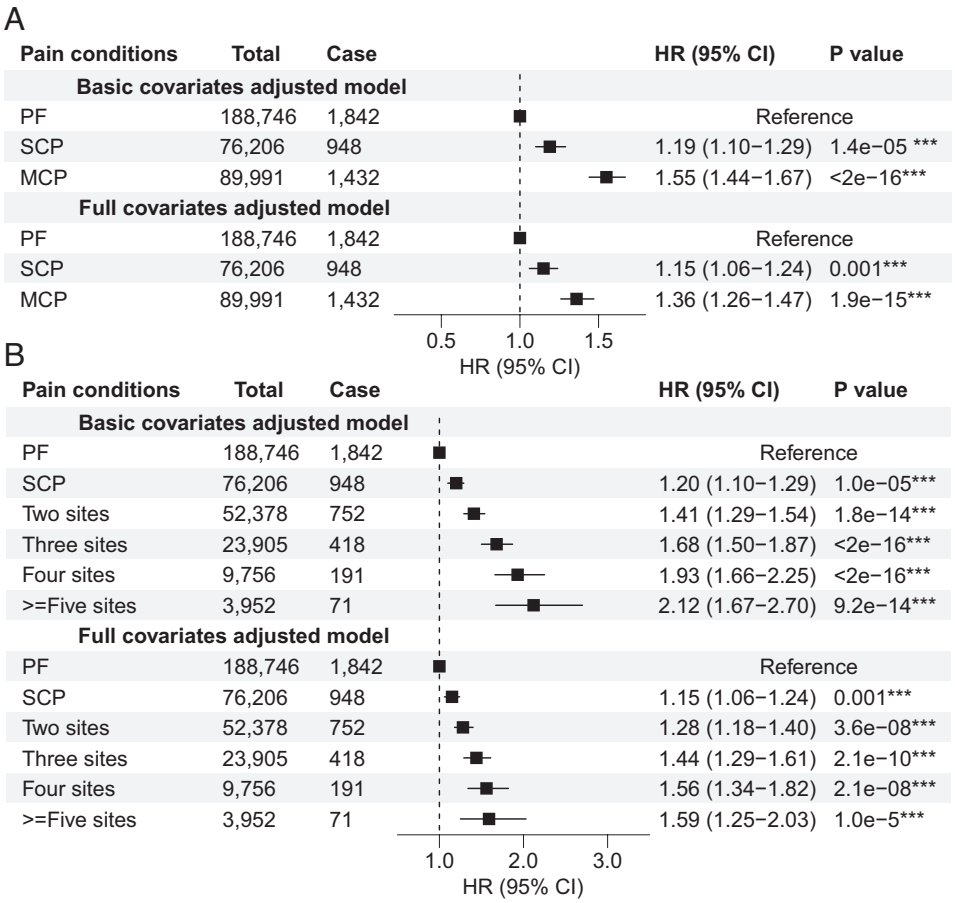

Fig. 1. Cox proportional hazards models for the association between numbers of coexisting CP sites and later dementia. The basic covariates adjusted model included age, gender, ethnicity, and medications (aspirin, ibuprofen, and paracetamol) as covariates. Full covariates adjusted model included age, gender, ethnicity, medications, Townsend deprivation index, educational attainment, BMI, smoking status, alcoholic drinking status, history of cancer, history of diabetes, history of vascular or heart problems (angina, hypertension, heart attack, and stroke), and ever seen a doctor for nervousness, anxiety, tension, or depression as covariates. The black squares and horizontal lines represent HRs and 95% CI, respectively, in the models. (*A*) Model for three categories of CP conditions. (*B*) Model for six categories of CP conditions. Both models supported the hypothesis that the risk of dementia was higher in individuals with more coexisting CP sites. Abbreviations: HR, hazard ratio; CI, confidence interval; PF, pain-free; SCP, single-site chronic pain; MCP, multisite chronic pain; Two sites, CP at two body sites; Three sites, CP at three body sites; Four sites, CP at four body sites; >=Five sites, CP at five or more body sites.

individuals with MCP demonstrated significantly accelerated aging trajectories (i.e., task performances declined faster) in the numeric memory test and TMT-b from either PF controls (numeric memory, $F = 6.957$, $P = 0.008$; TMT-b, $F = 8.412$, $P = 0.004$) or to individuals with SCP (numeric memory, $F = 6.383$, $P = 0.012$; TMT-b, $F = 5.250$, $P = 0.022$).

Multisite CP Was Accompanied by Hippocampal Volume Loss. We then established GAMs for total hippocampal gray matter volume (GMV) using the available image-derived phenotypes (IDPs, field IDs: 25886 and 25887) processed by the FMRIB's Automated Segmentation Tool (FAST) toolkit in the UK Biobank (51). Covariates included in the models were age, gender, medications, Townsend deprivation index, total brain volume (TBV), BMI, height, ethnicity, smoking status, alcoholic drinking status, and the first ten genetic principal components. Additionally, we tested the models without the adjustment of TBV since TBV decreases with aging (52). Significant group differences were found in the bilateral hippocampus, regardless of whether TBV was included as a covariate. Post-hoc analysis revealed that although the SCP individuals had lower hippocampal GMV when without the TBV adjustment (left hemisphere [lh]: $t = 2.373$, $P = 0.018$; right hemisphere [rh]: $t = 1.989$, $P = 0.047$) than PF controls, the volume loss was severer in the MCP individuals, as their bilateral hippocampus was significantly atrophied compared to the PF controls (without TBV: lh, $t = 4.635$, $P = 3.6 \times 10^{-6}$; lh, $t = 3.986$, $P = 6.8 \times 10^{-5}$; with TBV: lh, $t = 3.898$, $P = 9.8 \times 10^{-5}$; rh, $t = 3.134$, $P = 0.002$), and even to SCP individuals (without TBV: lh, $t = 2.468$, $P = 0.014$; rh, $t = 2.165$, $P = 0.030$; with TBV: lh, $t = 2.557$, $P = 0.011$; rh, $t = 2.226$, $P = 0.026$). No significant interactions between age and group were found in the fitting curves (Fig. 3*A*). We also performed additional analyses using the other two available IDPs (processed by FIRST [field IDs, 25019 and 25020] and AESG [field IDs, 26562 and 26593], respectively) for the bilateral hippocampal volumes (*SI Appendix*, Fig. S3 and Tables S4–S6).

Notably, we found that the hippocampal GMV loss aggravated along with the number of coexisting CP sites (Table 1). For illustration, the expected change in the left and right hippocampal GMV when shifting from PF to SCP (CP at one body site) was −9.795 mm^3 and −8.272 mm^3, respectively. In contrast, two-site MCP was associated with a reduction of 25.852 mm^3 and 22.202 mm^3 in the left and right hippocampal GMV, respectively. This hippocampal volume loss was up to 100.330 mm^3 and 87.522 mm^3 in individuals with CP at five or more body sites. We further examined the volume loss in the hippocampal subfields. Among 42 available IDPs, the bilateral CA3-head, right CA4-head, left hippocampal fissure, and left subiculum-body were significantly atrophied in

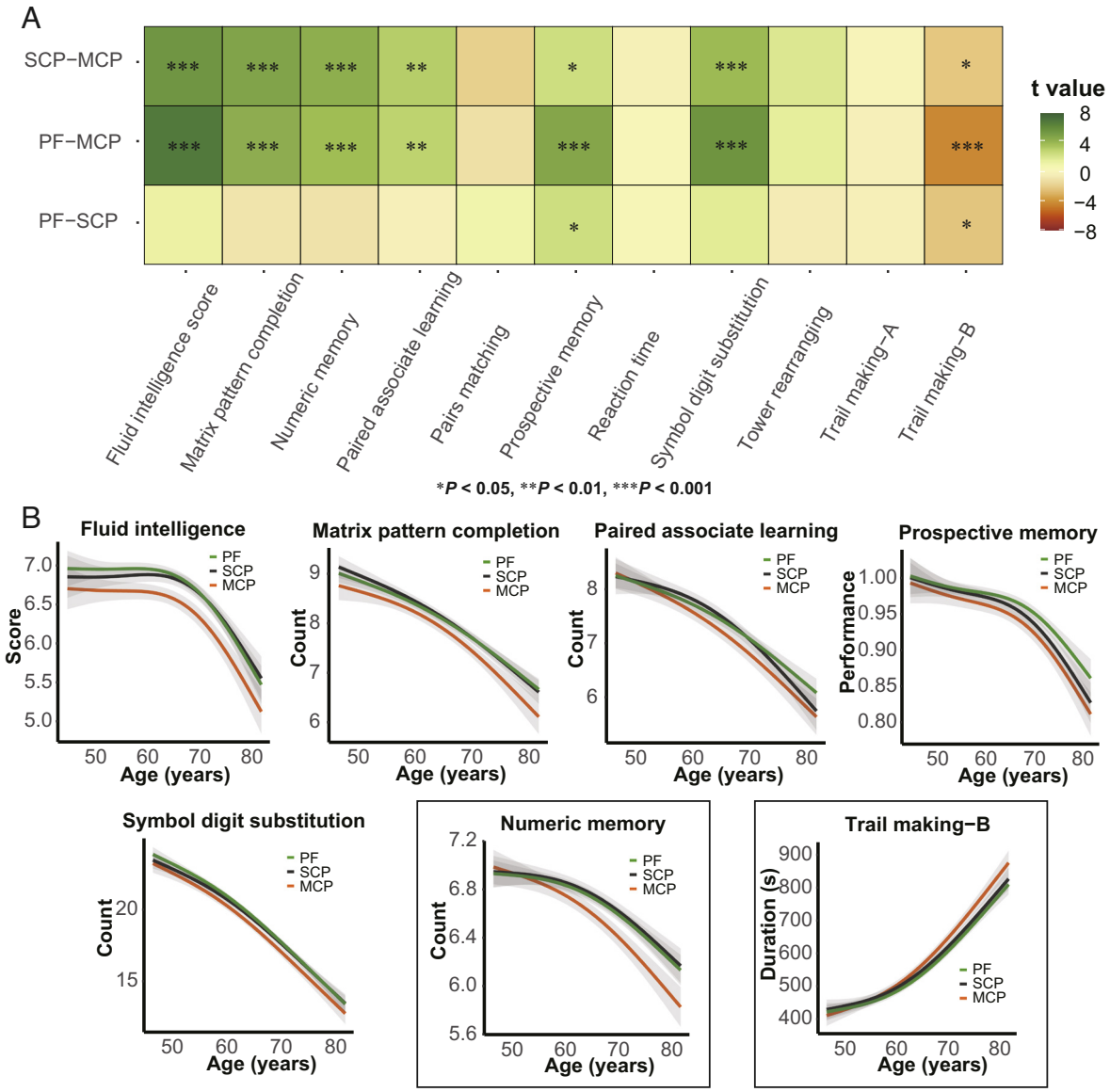

Fig. 2. Effect of three categories of CP conditions on cognitive tests. (*A*) Post-hoc results for the group differences in the cognitive test performances. Colors in the heatmap denote the magnitude of the *t*-value, and asterisks represent statistically significant effects: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, corrected for multiple comparisons. (*B*) Fitted aging trajectories of cognitive tests that performed significantly poorer in MCP. Intercept differences for the performance of eight cognitive tests are shown in part A. Test performances of numeric memory and trail making-B in MCP exhibit statistically accelerated aging trajectories compared to PF and SCP (noted with a black square frame). The shaded areas around the lines denote 95% CI. Abbreviations: PF, pain-free; SCP, single-site chronic pain; MCP, multisite chronic pain.

the MCP group after FDR correction (with covariates adjusted, including TBV) (Fig. 3*B*).

To investigate whether the bilateral hippocampal GMV loss underlined the cognitive decline in MCP, mediation analyses were performed. We found that the direct effects of MCP on fluid intelligence were significant (Fig. 3*C*, lh: β (c′) = −0.064, $P < 0.001$; rh: β (c′) = −0.065, $P < 0.001$), and bilateral hippocampal GMV partially mediated the effect of MCP on fluid intelligence (Fig. 3*C*, lh: β (a*b) = −0.002, $P = 0.006$; rh: β (a*b) = −0.001, $P = 0.024$), with age, gender, medications, Townsend deprivation index, TBV, BMI, height, ethnicity, smoking status, alcoholic drinking status, and 10 genetic principal components adjusted.

To quantify the detrimental effects of MCP on the hippocampus with accelerated aging, we equivalented the effect magnitudes of the differences in the hippocampal GMV between CP individuals and PF controls against the effects associated with aging for 60-y-old PF individuals (Table 1), given that age 60 was defined by the World Health Organization as the beginning of late adulthood (49). GAM-based regression was used to chart the normal aging trajectory of the hippocampal volume from all PF controls (n = 16,489) and contrast the differences between the normal aging trajectory and the trajectories of individuals with different CP conditions. For illustration, the expected effect associated with the differences between PF and SCP was equivalent to accelerated aging of 1.1 and 0.8 y for left and right hippocampal GMV, respectively, whereas the effect of two-site MCP was equivalent to accelerated aging of 2.7 and 2.2 y. In other words, the hippocampal GMV in a 60-y-old individual with two-site MCP (i.e., CP at two body sites) was similar to the volume of PF controls aged 62-y-old above. In summary, the hippocampal GMV in a 60-y-old individual with MCP (2 to 5 or more sites) was similar to the hippocampal GMV of PF controls aged from 62 to 68 y old (i.e., 2 to 8 y of accelerated aging).

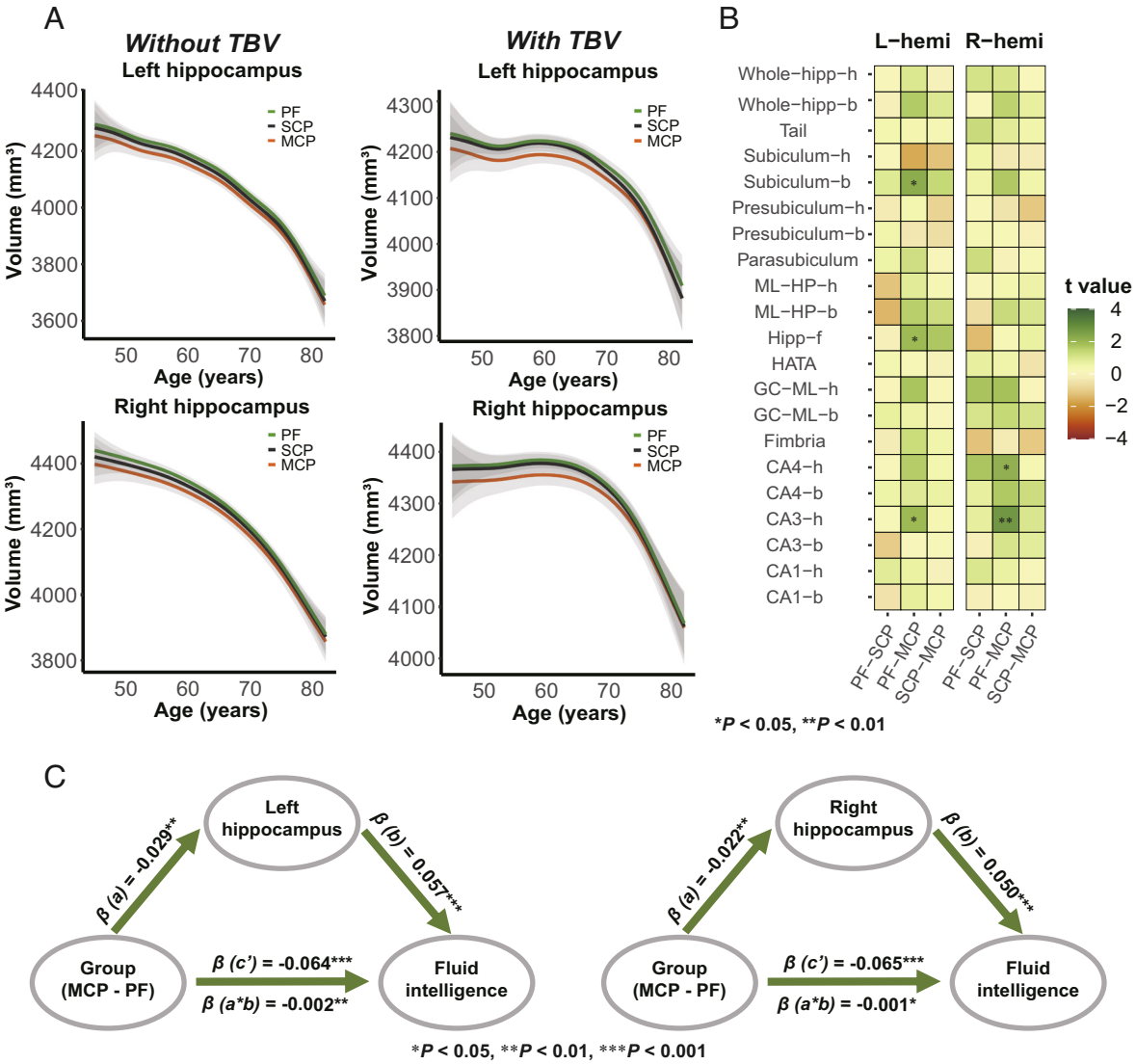

Fig. 3. Effect of three categories of CP conditions on hippocampal volume and its association with cognitive functions. (*A*) Aging trajectories for left and right total hippocampal GMVs in three categories of CP conditions. The left plots represent the model without TBV adjusted, and the right plots represent the model with TBV adjusted. The MCP demonstrates significantly lower bilateral total hippocampal GMV than both PF and SCP regardless of whether TBV was adjusted, whereas SCP only exhibits lower bilateral total hippocampal GMV than PF without the adjustment of TBV. No aging trajectory differences were detected. The shaded areas around the lines denote 95% CI. (*B*) Post-hoc results for the group differences in the hippocampal subfield volumes. Colors in the heatmap denote the magnitude of the *t*-value, and asterisks represent statistically significant effects: *$P < 0.05$, **$P < 0.01$, corrected for multiple comparisons. (*C*) The effect of MCP on fluid intelligence was partially mediated by bilateral total hippocampal GMV. Asterisks represent statistically significant effects: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. Abbreviations: TBV, total brain volume; L-Hemi, left hemisphere; R-Hemi, right hemisphere; h, head; b, body; Whole−hipp, whole hippocampal; Tail, hippocampal tail; ML−HP, molecular layer of the hippocampus; Hipp−f, hippocampal fissure; HATA, hippocampus amygdala transition area; GC−ML, granule cell and molecular layer of the dentate gyrus; PF, pain-free; SCP, single-site chronic pain; MCP, multisite chronic pain.

We also checked the specificity of hippocampal deterioration in MCP by running GAMs on the 72 cortical regions and 14 subcortical regions (*SI Appendix*, Fig. S4). We found that the bilateral hippocampus was the only subcortical region that demonstrated significant atrophy in MCP compared to PF and SCP after the FDR adjustment. Such results indicate that MCP did not lead to general brain deteriorations.

Discussion

Although there is a growing recognition that CP patients tend to report pain at multiple anatomical locations (16, 17), it is still unknown whether and to what extent MCP exerts burdens on patients' cognition and brain health. The present study revealed the impact of MCP on the risk of dementia and examined the abnormality of cognitive function and brain morphology in individuals with MCP. We found that MCP exhibited significantly higher dementia risk, broader and faster cognitive impairment, and greater hippocampal atrophy than both PF and SCP. Moreover, the detrimental effects of MCP on dementia risk and hippocampal volume aggravated along with the increased number of coexisting CP sites. Mediation analyses further revealed that the decline of fluid intelligence in MCP individuals was mediated by hippocampal atrophy.

Evaluating the HRs of later dementia in CP patients is crucial for early prevention and intervention. Consistent with previous longitudinal studies (8, 14, 15), we found an increased risk of dementia (1.15-fold higher) in individuals with CP at one body site (i.e., SCP) compared to PF with a larger sample (n = 354,943). However, the HR for SCP was relatively lower in comparison with other chronic conditions (30, 53, 54) or psychiatry disorders (53, 55, 56). Importantly, we found a higher dementia risk in

Table 1. Predicted equivalent effect of aging in terms of additional years for an average 60-y-old PF individual

Change in body site(s) of CP	Left hippocampus		Right hippocampus	
	Volume change (mm^3)	Equivalent aging at 60, y	Volume change (mm^3)	Equivalent aging at 60, y
PF- SCP	−9.795	1.1	−8.272	0.8
PF- Two sites	−25.825	2.7	−22.202	2.2
PF- Three sites	−33.255	3.3	−36.042	3.4
PF- Four sites	−73.660	6.2	−46.175	4.2
PF- >=Five sites	−100.330	7.7	−87.522	7.1

Abbreviations: PF, pain-free; SCP, single-site chronic pain; Two sites, CP at two body sites; Three sites, CP at three body sites; Four sites, CP at four body sites; >=Five sites, CP at five or more body sites.

individuals with MCP than in both PF (1.36-fold) and SCP (1.19-fold). The effect magnitude for MCP was modestly higher than diabetes (53, 54) and coronary heart disease (30). With Cox models that included six categories of CP conditions, we further confirmed that the observed increased dementia risk was explained by the number of coexisting CP sites (i.e., the risk of dementia increased along with the number of coexisting CP sites) and, in particular, the dementia risk for individuals with CP at five or more body sites was 1.59-fold higher than that for PF participants. Such effect magnitude was comparable to heart failure (30), post-traumatic stress disorder (55), and depression (56). In summary, our results revealed a heavy burden of dementia risk for MCP as compared to other chronic conditions or mental disorders and highlighted a necessity for preventing cognitive decline in MCP patients.

In addition to the increased dementia risk, the present study also found that individuals with MCP were accompanied by impaired cognitive performances. Consistent with previous findings (3, 4), individuals with SCP showed deficits in tasks requiring memory, learning, attention, and executive functions (3, 4, 57, 58), as reflected by impaired task performance on prospective memory and TMT-b, in comparison to PF controls. For individuals with MCP, in addition to the three tests aforementioned, they also performed worse than both PF controls and SCP individuals in the tests of fluid intelligence, matrix pattern completion, numeric memory, paired associative learning, and symbol digit substitution (Fig. 2*A*). These tests were reported to be associated with dementia in previous studies (59–64), suggesting a potential association between observed cognitive decline and the increased risk of dementia in MCP. Moreover, we found that the task performances of the TMT-b and numeric memory, measuring short-term memory (65), executive control, and cognitive flexibility (57), exhibited an accelerated age-related deterioration in individuals with MCP compared to PF controls and those with SCP.

Previous studies investigating the brain morphologies in CP have yielded inconsistent findings regarding the hippocampal volume (44, 45, 66–68), even with meta-analyses (33, 34). Researchers argued that the inconsistency might arise from the heterogeneity of CP and the limited effect size of CP on hippocampal volume. With a larger sample size (n = 5,597), we found that SCP did not exhibit significant atrophy in total hippocampal GMV after adjusting the whole covariates, as previous evidence showed that the hippocampus shrank only in certain subtypes of CP, such as trigeminal neuralgia and chronic back pain (44, 45, 66, 67), which have been frequently reported to be overlapped with other CP conditions (18, 69). In contrast to the highly heterogeneous results from SCP patients, MCP demonstrated significant bilateral total hippocampal GMV loss either compared to PF or SCP. We also found that the effect of the hippocampal GMV loss aggravated along with the number of coexisting CP sites, in line with what we observed in dementia risk, indicating a potential association. Importantly, we demonstrated that the detrimental effect of MCP on brain volume was relatively specific to the hippocampus but not a general deterioration (*SI Appendix*, Fig. S4). These results not only highlighted the strong effect of MCP on hippocampal volume, but also supported a recent genome-wide study linking MCP and hippocampal abnormality with the DCC gene, which is responsible for axonogenesis and mainly expressed in the hippocampus (18). In the analysis of hippocampal subfields, we found significant GMV loss in the bilateral CA3-head, right CA4-head, left hippocampal fissure, and left subiculum-body, all of which were demonstrated to be dementia related (41, 70–72). Also, in line with our findings on cognitive functions, these hippocampal subfield regions were critical to the maintenance of learning (73), memory (74, 75), executive functions (27, 71), and cognitive flexibility (71).

Taking advantage of the unprecedented large-scale MRI data, the current study was able to quantify and benchmark the effect of MCP on hippocampal volume. Since the hippocampal volume reduces during normal aging, we equivalented the effect magnitudes of MCP on hippocampal atrophy to the aging effect on an average 60-y-old PF individual. The hippocampal GMV demonstrated an up-to-8-y aging effect in individuals with CP at five or more body sites. A recent study demonstrated that heavy drinkers might have an up-to-9-y aging effect based on global gray matter deterioration in 50-y-old individuals (76). Given that age 60 marked the start of late adulthood, an age at which the rate of brain volume loss was the fastest throughout life (49), the heavily reduced hippocampal volume reflected accelerated brain aging and might be the underlying cause of a series of age-related cognitive burdens and dementia risk.

With mediation analyses, we found that the bilateral hippocampal volume significantly mediated the effect of MCP on fluid intelligence. Since fluid intelligence measures the general cognitive ability (77), hippocampal volume reduction in MCP might underlie the overall cognitive decline instead of impairment in a single cognitive domain. It should be noted that the observed mediation effect was relatively subtle; this was commonly identified in large-scale neuroimage studies (78) examining whether the effect of exposure on a certain outcome could be explained by brain morphology (79). In our study, we performed a relatively stringent exclusion criterion while adjusting multiple potential confounders for more accurate detection of cognitive impairment and brain atrophy associated with MCP. Thus, the observed effect might be biologically meaningful, and future studies should develop a causal relationship with longitudinal designs. Taken together, our results suggested that cognitive decline and hippocampal atrophy interact biologically and may underlie the elevated dementia risks in MCP.

There are several limitations in the current study. First, the CP conditions were self-reported. Detailed clinical evaluations of the course and severity of CP and the duration of the pain medication use were not available. Second, the detrimental effects of MCP

on cognitive functions and hippocampal volume were detected with cross-sectional data. Causal relationships need to be further studied with longitudinal designs. Third, due to insufficient dementia cases diagnosed after the first brain imaging assessment, we were not able to establish a direct association between dementia and cognitive functions or hippocampal volume.

In conclusion, the present study integrated the negative impacts of MCP on cognition and the hippocampus, providing evidence that cognitive decline and hippocampal atrophy interact biologically and may underlie the elevated dementia risks in MCP. Our findings indicated a potential benefit of taking the number of overlapping pain conditions into account in both basic investigations and clinical decisions.

Materials and Methods

Participants. Data used in the study were from the UK Biobank with application ID 71901. All 502,467 participants in UK Biobank provided written, informed consent, and the study was approved by the North West Multi-centre Research Ethics Committee.

In the analyses of the dementia risk, we included 354,943 participants without CP all over the body or prevalent dementia, and with complete covariate data from the initial assessment visit (n = 502,467).

A subset of participants from the initial assessment visit was invited to the imaging assessment. In the analyses of cognitive functions and hippocampal volumes, we included 26,407 individuals with brain MRI data while excluding those with severe diseases, neurological problems, psychiatric disorders, or CP all over the body (*SI Appendix*, Fig. S1). Imbalances in age and gender ratio between CP and PF groups were controlled with a matching process (*SI Appendix*).

Dementia Assessment. Dementia cases were identified using the International Classification of Diseases-10 codes (i.e., F00, F01, F02, F03, or G30) generated by the UK Biobank. Prevalent dementia cases, defined as individuals with preexisting dementia at baseline or those who developed dementia during the first 2 y of follow-up, were excluded from our sample, as it might lead to reverse-causation bias. Right censoring occurred at the first date of death, loss of follow-up, or on March 18, 2021 (the last hospital admission date), whichever came first before the dementia was recorded.

Pain Assessment. Pain conditions were assessed via a touchscreen question: "In the last month have you experienced any of the following that interfered with your usual activities." Participants were able to select from the following categories: back pain, facial pain, headaches, knee pain, stomach/abdominal pain, hip pain, neck/shoulder pain, none of the above, prefer not to answer, or pain all over the body. If any of the pain types were selected, the participants were then asked to report whether each selected type of pain lasted for more than 3 mo. If the participants reported that they had pain all over the body, information about specific pain sites would not be recorded. Depending on their responses, individuals with more than one body site of pain lasting longer than 3 mo were considered as having MCP, those with only one body site of pain that lasted longer than 3 mo were included in the group of SCP, and those who reported no pain experienced last month were defined as PF controls. Participants with CP all over the body were excluded from our main analyses because lacking information about pain sites.

Cognitive Assessment. Cognitive tests were administered with a touchscreen interface in the UK Biobank Assessment Centre at the first brain imaging assessment. The eleven available tests included in this study were: reaction time, numeric memory, fluid intelligence, trail-making A (TMT-a), TMT-b, matrix pattern completion, tower rearranging, symbol digit substitution, paired associate learning, prospective memory, and pairs matching.

Structural MRI Data. Available and quality-controlled T1-weighted IDPs (details in https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/brain_mri.pdf) were used in the current study. The total bilateral hippocampal GMVs (field IDs, 25886 and 25887) used in the current study were processed with FAST (80). The 42 bilateral subfield hippocampal IDPs (field IDs, 26620 - 26663) were defined by the Freesurfer subsegmentation atlas (81). Individuals with IDP values outside the range of four SDs were excluded from the data analysis.

Statistical Analyses.

Risk of dementia estimation. Cox proportional hazards regression models were used to estimate the risk of dementia in individuals with different numbers of coexisting CP sites. The duration of follow-up (subtract the date of recruitment from the first date of dementia, death, loss of follow-up, or on March 18, 2021 [the last hospital admission date] whichever came first) was calculated as the timescale and the PF was set as the reference group. The fundamental assumption of the Cox model is the proportional hazards assumption, which assumes that the relative hazard is constant over time with different covariate levels (50). We utilized the Schoenfeld residuals method (50), which tested the nonzero slope of each time-dependent covariate in the Cox model, to check the assumption. We generated models for three (i.e., PF, SCP, and MCP) and six (i.e., PF, SCP, and CP at 2 to 5 or more body sites; we merged individuals who reported CP at five or more body sites into one group, given its limited sample size) categories of CP conditions separately. The model was first minimally adjusted for age, sex, ethnicity, and medications. The fully adjusted model additionally controlled for Townsend deprivation index (a measure of socioeconomic status), educational attainment, BMI, smoking status, alcoholic drinking status, history of cancer, history of diabetes, history of vascular or heart problems (angina, hypertension, heart attack, and stroke), and ever seen a doctor for nervousness, anxiety, tension, or depression that can be potential confounders. The results of the models were presented as HRs and 95% CI, representing the averaged ratio of hazard of dementia between CP conditions within 11.8 y of follow-up. Analyses of dementia risk were performed in R 4.1.2 (82) with the "survival" package (83).

Assessment of group differences in cognitive functions and brain structures. The GAMs for cognitive functions and hippocampal IDPs were established with the following formula: $VAR \sim group + s\left(age\right) + s\left(age,\ by = group\right) + COV$, where *VAR* represents the task performance of the cognitive functions or hippocampal GMV. We established models for each cognitive test and bilateral total hippocampal GMV separately. The *s()* term estimates the smooth effect based on the thin-plate regression splines combining *k* number of nonlinear basis functions. The number of base functions *k* was determined based on the model fit. The first smoothed term in the model calculates the overall nonlinear effect of age on the cognitive functions or hippocampal GMV, while the smoothed term with *by* argument is the function of smooth-factor interactions, which estimates the unique effect of age for each of the three CP groups. The *group* and *COV* are the parametric terms in the model: the former estimates the intercepts for the three categories of CP conditions, and the latter is the covariates to be controlled in this model. We included age, gender, medications, Townsend deprivation index, BMI, height, ethnicity, smoking status, alcoholic drinking status, and the first ten genetic principal components in all of the GAMs. The genetic principal components in the models were used to control the potential effect of population stratification since allele frequency differences between cases and controls due to systematic ancestry differences can cause spurious associations in disease studies (84). Models for hippocampal GMV additionally adjusted TBV to account for the between-subject variations in the overall brain morphologies. The effect of interest outputted by GAMs includes the effect of intercepts (i.e., group difference) and smooth terms. The group differences in the intercepts are manifested in the *P* value for the *group* term, the smooth effect for each group is centered around zero, as such, the *P* value for the smooth term indicates whether there are significant differences in the aging trajectories, both of which are of our research interests. Smooth effects of cognitive functions and hippocampal GMV were graphed with fitted GAM curves and 95% CI. Analyses of hippocampal subfields and whole-brain IDPs were examined using GAMs with intercept differences as the effect of interests (without smooth terms), and covariates were the same as for hippocampal GAMs. Intercept results for 11 cognitive tests and hippocampal subfields were plotted with heatmaps. The analyses were conducted in R 4.1.2 (82). GAMs were modeled with the "mgcv" package (85), and visualizations were performed with the "ggplot2" package (86). *P* values were FDR corrected.

Assessment of hippocampal GMV loss with different number of coexisting CP sites. To quantify the effect of different numbers of coexisting CP sites on total hippocampal GMV, we divided the MCP group into four categories (i.e., individuals with CP at 2 to 5 or more body sites) and generated age- and gender-matched PF controls for each group. After regressing out the effect of the covariates (including TBV), we calculated the expected residual differences in the hippocampal GMV between participants with different numbers of coexisting CP sites and PF controls and, then, equivalented the effect magnitudes between CP participants and PF controls against the effects associated with aging for 60-y-old PF individuals, given age 60 was defined as the beginning of late adulthood (49). The normal aging effect on hippocampal GMV to be referenced was estimated on the whole PF sample (n = 16,489) with age, gender, medications, Townsend deprivation index, BMI, height, ethnicity, smoking status, alcoholic drinking status, and the first 10 genetic principal components adjusted. GAMs for modeling hippocampal aging trajectories were established in R 4.1.2 (82) with the "mgcv" package (85).

Multicategorical mediation analyses. Mediation analyses were conducted to investigate whether the effect of three categories of CP conditions on cognitive function was mediated by total hippocampal GMV. Effects of age, gender, medication, Townsend deprivation index, BMI, height, ethnicity, smoking status, alcoholic drinking status, and the first ten genetic principal components were adjusted for each model. As the CP condition was a multicategorical independent variable, we established the mediation models for each of all the three group pairs separately (i.e., PF vs. SCP, PF vs. MCP, and SCP vs. MCP), and the indirect effects (a*b) were corrected with the FDR method (87). Mediation analyses were conducted in R 4.1.2 (82) with the "lavaan" package (88).

Data, Materials, and Software Availability. This project corresponds to UK Biobank application ID 71901. The health-related outcome, cognitive tests, and neuroimaging data from the UK Biobank are available at https://biobank.ndph.ox.ac.uk/ by application. Scripts used to conduct the analyses are available at https://github.com/tulab-brain/Multisite-chronic-pain.

ACKNOWLEDGMENTS. We sincerely thank all participants and researchers from the UK Biobank. The study was supported by the STI2030-Major Projects (2022ZD0206400); National Natural Science Foundation of China (32171078); the Scientific Foundation of the Institute of Psychology, Chinese Academy of Sciences (E0CX52, E2CX4015); and Young Elite Scientist Sponsorship Program by the China Association for Science and Technology (E1KX0210). X.L. is supported by a grant from the Youth Innovation Promotion Association, Chinese Academy of Sciences.

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1. S. P. Cohen, L. Vase, W. M. Hooten, Chronic pain: An update on burden, best practices, and new advances. *Lancet* **397**, 2082–2097 (2021).
2. J. Dahlhamer *et al.*, Prevalence of chronic pain and high-impact chronic pain among adults–United States, 2016. *MMWR Morb. Mortal. Wkly. Rep.* **67**, 1001–1006 (2018).
3. D. M. Higgins, A. M. Martin, D. G. Baker, J. J. Vasterling, V. Risbrough, The relationship between chronic pain and neurocognitive function: A systematic review. *Clin. J. Pain* **34**, 262–275 (2018).
4. O. Moriarty, B. E. McGuire, D. P. Finn, The effect of pain on cognitive function: A review of clinical and preclinical research. *Prog. Neurobiol.* **93**, 385–404 (2011).
5. C. E. Phelps, E. Navratilova, F. Porreca, Cognition in the chronic pain experience: Preclinical insights. *Trends Cogn. Sci.* **25**, 365–376 (2021).
6. W. Y. Gong *et al.*, Chronic monoarthritis pain accelerates the processes of cognitive impairment and increases the NMDAR subunits NR2B in CA3 of hippocampus from 5-month-old transgenic APP/PS1 Mice. *Front. Aging Neurosci.* **9**, 123 (2017).
7. I. Rouch *et al.*, Association between chronic pain and long-term cognitive decline in a population-based cohort of elderly participants. *Pain* **162**, 552–560 (2021).
8. E. L. Whitlock *et al.*, Association between persistent pain and memory decline and dementia in a longitudinal cohort of elders. *JAMA Intern. Med.* **177**, 1146–1153 (2017).
9. Z. Arvanitakis, R. C. Shah, D. A. Bennett, Diagnosis and management of dementia: Review. *JAMA* **322**, 1589–1599 (2019).
10. G. McKhann *et al.*, Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. *Neurology* **34**, 939–944 (1984).
11. R. S. Wilson, S. E. Leurgans, P. A. Boyle, J. A. Schneider, D. A. Bennett, Neurodegenerative basis of age-related cognitive decline. *Neurology* **75**, 1070 (2010).
12. L. L. Smits *et al.*, Trajectories of cognitive decline in different types of dementia. *Psychol. Med.* **45**, 1051–1059 (2015).
13. K. E. Innes, U. Sambamoorthi, The potential contribution of chronic pain and common chronic pain conditions to subsequent cognitive decline, new onset cognitive impairment, and incident dementia: A systematic review and conceptual model for future research. *J. Alzheimers Dis.* **78**, 1177–1195 (2020).
14. S.-W. Huang *et al.*, Osteoarthritis increases the risk of dementia: A nationwide cohort study in Taiwan. *Sci. Rep.* **5**, 10145 (2015).
15. P. H. Kao *et al.*, Chronic pain increases the risk of dementia: A nationwide population-based cohort study. *Pain Physician* **24**, E849–E856 (2021).
16. A. Schrepf *et al.*, ICD-10 codes for the study of chronic overlapping pain conditions in administrative databases. *J. Pain* **21**, 59–70 (2020).
17. W. Maixner, R. B. Fillingim, D. A. Williams, S. B. Smith, G. D. Slade, Overlapping chronic pain conditions: Implications for diagnosis and classification. *J. Pain* **17**, T93–T107 (2016).
18. S. Khoury *et al.*, Genome-wide analysis identifies impaired axonogenesis in chronic overlapping pain conditions. *Brain* **145**, 1111–1123 (2022).
19. C. Tanguay-Sabourin *et al.*, A data-driven biopsychosocial framework determining the spreading of chronic pain. *medRxiv [Preprint]* (2022). https://doi.org/10.1101/2022.07.22.22277850 (Accessed 8 August 2022).
20. K. J. A. Johnston *et al.*, Genome-wide association study of multisite chronic pain in UK Biobank. *PLoS Genet.* **15**, e1008164 (2019).
21. J. Zhu *et al.*, Multisite chronic pain as a causal risk factor for coronary artery disease: Findings from Mendelian randomization. *Pain*, 10.1097/j.pain.0000000000002732 (2022).
22. M. G. Page, M. Fortier, M. A. Ware, M. Choiniere, As if one pain problem was not enough: Prevalence and patterns of coexisting chronic pain conditions and their impact on treatment outcomes. *J. Pain Res.* **11**, 237–254 (2018).
23. A. L. Byers, K. Yaffe, Depression and risk of developing dementia. *Nat. Rev. Neurol.* **7**, 323–331 (2011).
24. M. S. Greenberg, K. Tanev, M. F. Marin, R. K. Pitman, Stress, PTSD, and dementia. *Alzheimers Dement.* **10**, S155–S165 (2014).
25. P. L. Rock, J. P. Roiser, W. J. Riedel, A. D. Blackwell, Cognitive impairment in depression: A systematic review and meta-analysis. *Psychol. Med.* **44**, 2029–2040 (2014).
26. J. E. Galvin, K. Uryu, V.M.-Y. Lee, J. Q. Trojanowski, Axon pathology in Parkinson's disease and Lewy body dementia hippocampus contains α-, β-, and γ-synuclein. *Proc. Natl. Acad. Sci. U.S.A.* **96**, 13450–13455 (1999).
27. T. E. Evans *et al.*, Subregional volumes of the hippocampus in relation to cognitive function and risk of dementia. *Neuroimage* **178**, 129–135 (2018).
28. M. H. Chen *et al.*, Risk of dementia among patients with asthma: A nationwide longitudinal study. *J. Am. Med. Dir. Assoc.* **15**, 763–767 (2014).
29. M. Kivimaki *et al.*, Body mass index and risk of dementia: Analysis of individual-level data from 1.3 million individuals. *Alzheimers Dement.* **14**, 601–609 (2018).
30. F. J. Wolters *et al.*, Coronary heart disease, heart failure, and the risk of dementia: A systematic review and meta-analysis. *Alzheimers Dement.* **14**, 1493–1504 (2018).
31. F. Irani, J. M. Barbone, J. Beausoleil, L. Gerald, Is asthma associated with cognitive impairments? A meta-analytic review. *J. Clin. Exp. Neuropsychol.* **39**, 965–978 (2017).
32. A. K. Nair *et al.*, Asthma amplifies dementia risk: Evidence from CSF biomarkers and cognitive decline. *Alzheimers Dement. (N. Y.)* **8**, e12315 (2022).
33. R. F. Smallwood *et al.*, Structural brain anomalies and chronic pain: A quantitative meta-analysis of gray matter volume. *J. Pain* **14**, 663–675 (2013).
34. Y. Tu, J. Cao, Y. Bi, L. Hu, Magnetic resonance imaging for chronic pain: Diagnosis, manipulation, and biomarkers. *Sci. China Life Sci.* **64**, 879–896 (2021).
35. Y. Tu *et al.*, Distinct thalamocortical network dynamics are associated with the pathophysiology of chronic low back pain. *Nat. Commun.* **11**, 3948 (2020).
36. S. Cao, D. W. Fisher, T. Yu, H. Dong, The link between chronic pain and Alzheimer's disease. *J. Neuroinflammation* **16**, 204 (2019).
37. F. Marchand, M. Perretti, S. B. McMahon, Role of the immune system in chronic pain. *Nat. Rev. Neurosci.* **6**, 521–532 (2005).
38. K. Zorina-Lichtenwalter *et al.*, Identification and characterization of genetic risk shared across 24 chronic pain conditions in the UK Biobank. medRxiv [Preprint] (2022), https://doi.org/10.1101/2022.06.28.22277025 (Accessed 5 August 2022).
39. C. M. Bird, N. Burgess, The hippocampus and memory: Insights from spatial processing. *Nat. Rev. Neurosci.* **9**, 182–194 (2008).
40. J. R. Whitlock, A. J. Heynen, M. G. Shuler, M. F. Bear, Learning induces long-term potentiation in the hippocampus. *Science* **313**, 1093–1097 (2006).
41. L. G. Apostolova *et al.*, Subregional hippocampal atrophy predicts Alzheimer's dementia in the cognitively normal. *Neurobiol. Aging* **31**, 1077–1088 (2010).
42. M. E. Dounavi *et al.*, Volumetric alterations in the hippocampal subfields of subjects at increased risk of dementia. *Neurobiol. Aging* **91**, 36–44 (2020).
43. C. R. Jack *et al.*, Antemortem MRI findings correlate with hippocampal neuropathology in typical aging and dementia. *Neurology* **58**, 750 (2002).
44. A. A. Mutso *et al.*, Abnormalities in hippocampal functioning with persistent pain. *J. Neurosci.* **32**, 5747–5756 (2012).
45. A. Noorani *et al.*, Pain relief reverses hippocampal abnormalities in trigeminal neuralgia. *J. Pain* **23**, 141–155 (2022).
46. D. R. Cox, Regression models and life-tables. *J. R. Statist. Soc.: Ser. B Methodol.* **34**, 187–202 (1972).
47. M. J. Stensrud, M. A. Hernan, Why test for proportional hazards? *JAMA* **323**, 1401–1402 (2020).
48. S. N. Wood, *Generalized Additive Models: An Introduction with R* (Chapman and Hall/CRC, 2006).
49. R. A. I. Bethlehem *et al.*, Brain charts for the human lifespan. *Nature* **604**, 525–533 (2022).
50. D. Schoenfeld, Partial residuals for the proportional hazards regression model. *Biometrika* **69**, 239–241 (1982).
51. K. L. Miller *et al.*, Multimodal population brain imaging in the UK Biobank prospective epidemiological study. *Nat. Neurosci.* **19**, 1523–1536 (2016).
52. S. Nerland *et al.*, A comparison of intracranial volume estimation methods and their cross-sectional and longitudinal associations with age. *Hum. Brain Mapp.* **43**, 4620–4639 (2022), 10.1002/hbm.25978.
53. W. Katon *et al.*, Effect of depression and diabetes mellitus on the risk for dementia: A national population-based cohort study. *JAMA Psychiatry* **72**, 612–619 (2015).

54. N. N. Haroon *et al.*, Risk of dementia in seniors with newly diagnosed diabetes: A population-based study. *Diabetes Care* **38**, 1868–1875 (2015).
55. M. M. Gunak *et al.*, Post-traumatic stress disorder as a risk factor for dementia: Systematic review and meta-analysis. *Br. J. Psychiatry* **217**, 600–608 (2020).
56. L. Yang *et al.*, Depression, depression treatments, and risk of incident dementia: A prospective cohort study of 354,313 participants. *Biol. Psychiatry*, 10.1016/j.biopsych.2022.08.026 (2022).
57. C. R. Bowie, P. D. Harvey, Administration and interpretation of the trail making test. *Nat. Protoc.* **1**, 2277–2281 (2006).
58. G. O. Einstein, M. A. McDaniel, Prospective memory: Multiple retrieval processes. *Curr. Dir. Psychol. Sci.* **14**, 286–290 (2005).
59. K. D. Harrington *et al.*, The effect of preclinical Alzheimer's disease on age-related changes in intelligence in cognitively normal older adults. *Intelligence* **70**, 22–29 (2018).
60. H. Amieva, C. Meillon, C. Proust-Lima, J. F. Dartigues, Is low psychomotor speed a marker of brain vulnerability in late life? Digit symbol substitution test in the prediction of Alzheimer, Parkinson, stroke, disability, and depression. *Dement Geriatr. Cogn. Disord.* **47**, 297–305 (2019).
61. A. Egerhazi, R. Berecz, E. Bartok, I. Degrell, Automated neuropsychological test battery (CANTAB) in mild cognitive impairment and in Alzheimer's disease. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **31**, 746–751 (2007).
62. P. Chen *et al.*, Cognitive tests that best discriminate between presymptomatic AD and those who remain nondemented. *Neurology* **55**, 1847 (2000).
63. G. Smith, S. Della Sala, R. H. Logie, E. A. Maylor, Prospective and retrospective memory in normal ageing and dementia: A questionnaire study. *Memory* **8**, 311–321 (2000).
64. D. Street, D. Whiteside, T. Rittman, J. B. Rowe, Prodromal markers of neurodegenerative disease: Insights from the UK biobank dataset. *Alzheimer's Dementia.* **17**, e049865 (2021).
65. J. B. Hale, J.-A.B. Hoeppner, C. A. Fiorello, Analyzing digit span components for assessment of attention processes. *J. Psychoeducational Assess.* **20**, 128–143 (2002).
66. M. F. Vaculik, A. Noorani, P. S. Hung, M. Hodaie, Selective hippocampal subfield volume reductions in classic trigeminal neuralgia. *Neuroimage Clin.* **23**, 101911 (2019).
67. E. Vachon-Presseau *et al.*, The stress model of chronic pain: Evidence from basal cortisol and hippocampal structure and function in humans. *Brain* **136**, 815–827 (2013).
68. S. D. Tagliaferri *et al.*, Brain structure, psychosocial, and physical health in acute and chronic back pain: A UK Biobank study. *Pain* **163**, 1277–1290 (2022).
69. J. S. Koopman *et al.*, Incidence of facial pain in the general population. *Pain* **147**, 122–127 (2009).
70. K. Kwak *et al.*, Differential role for hippocampal subfields in Alzheimer's disease progression revealed with deep learning. *Cereb. Cortex.* **32**, 467–478 (2022).
71. S. S. Shahid *et al.*, Hippocampal-subfield microstructures and their relation to plasma biomarkers in Alzheimer's disease. *Brain* **145**, 2149–2160 (2022).
72. A. J. Bastos-Leite *et al.*, Hippocampal sulcus width and cavities: Comparison between patients with Alzheimer disease and nondemented elderly subjects. *Am. J. Neuroradiol.* **27**, 2141–2145 (2006).
73. N. A. Suthana *et al.*, High-resolution 7T fMRI of human hippocampal subfields during associative learning. *J. Cogn. Neurosci.* **27**, 1194–1206 (2015).
74. R. P. Kesner, I. Lee, P. Gilbert, A behavioral assessment of hippocampal function based on a subregional analysis. *Rev. Neurosci.* **15**, 333–352 (2004).
75. M. A. Yassa *et al.*, High-resolution structural and functional MRI of hippocampal CA3 and dentate gyrus in patients with amnestic mild cognitive impairment. *Neuroimage* **51**, 1242–1252 (2010).
76. R. Daviet *et al.*, Associations between alcohol consumption and gray and white matter volumes in the UK Biobank. *Nat. Commun.* **13**, 1175 (2022).
77. J. R. Gray, C. F. Chabris, T. S. Braver, Neural mechanisms of general fluid intelligence. *Nat. Neurosci.* **6**, 316–322 (2003).
78. S. M. Smith, T. E. Nichols, Statistical challenges in "big data" human neuroimaging. *Neuron* **97**, 263–268 (2018).
79. Y. Li *et al.*, The brain structure and genetic mechanisms underlying the nonlinear association between sleep duration, cognition and mental health. *Nat. Aging* **2**, 425–437 (2022).
80. Y. Zhang, M. Brady, S. Smith, Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans. Med. Imaging* **20**, 45–57 (2001).
81. J. E. Iglesias *et al.*, A computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: Application to adaptive segmentation of in vivo MRI. *Neuroimage* **115**, 117–137 (2015).
82. R. C. Team, *R: A Language and Environment for Statistical Computing* (R Foundation for Statistical Computing, Vienna, Austria, 2021).
83. T. Therneau, A Package for Survival Analysis in S (R package version 2, 2015).
84. A. L. Price *et al.*, Principal components analysis corrects for stratification in genome-wide association studies. *Nat. Genet.* **38**, 904–909 (2006).
85. S. N. Wood, *Generalized Additive Models: An Introduction with R* (Chapman and Hall/CRC, ed. 2, 2017).
86. H. Wickham, *ggplot2: Elegant Graphics for Data Analysis, Use R!* (Springer International Publishing, Cham, ed. 2, 2016), 10.1007/978-3-319-24277-4.
87. A. F. Hayes, K. J. Preacher, Statistical mediation analysis with a multicategorical independent variable. *Br. J. Math. Stat. Psychol.* **67**, 451–470 (2014).
88. Y. Rosseel, lavaan: An R package for structural equation modeling. *J Stat. Softw.* **48**, 1–36 (2012).