Published in final edited form as:

PM R. 2013 June ; 5(6): 471–480. doi:10.1016/j.pmrj.2013.03.004.

White Matter Hyperintensity Burden and Disability in Older Adults: Is Chronic Pain a Contributor?

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N.B. Disclosure: nothing to disclose

M.W.H. Disclosure related to this publication: grant, Claude Pepper Older Americans Independence Center Intramural Research Program of the NIH, National Institute on Aging

Disclosures outside this publication: expert testimony, (money to institution) Worker's Compensation, Personal Injury; grants, NIH 1R56NS07089-01, NIH R21HD067906-01

H.A. Disclosure related to this publication: grant, NIH

Disclosure outside this publication: grant, NIH

C.R. Disclosure related to this publication: grant, NIA/NINDS, 1 R01 AG029232-01

K.D.E. Disclosure: nothing to disclose

S.P. Disclosure related to this publication: grant, NIH

Disclosure outside this publication: grants/grants pending, Merck, Eli Lilly, Ortho Biotech, Teva

L.M. Disclosure related to this publication: grant, Claude Pepper Older Americans Independence Center Intramural Research Program of the NIH, National Institute on Aging Disclosures outside this publication: expert testimony, (money to institution) Mental Status Competency; grants/grants pending, R01 AG034078, RC3 AG 037357

S.T. Disclosure: nothing to disclose

V.V. Disclosure: nothing to disclose

D.W. Disclosure: nothing to disclose

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Peer reviewers and all others who control content have no relevant financial relationships to disclose.

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Abstract

Objective—To primarily explore differences in global and regional white matter hyperintensities (WMH) in older adults with self-reported disabling and nondisabling chronic low back pain (CLBP) and to examine the association of WMH with gait speed in all participants with CLBP. To secondarily compare WMH of the participants with CLBP with the pain-free controls.

Design—A cross-sectional, case-control study.

Setting—University of Pittsburgh.

Participants—Twenty-four community-dwelling older adults: 8 with self-reported disabling CLBP, 8 with nondisabling CLBP, and 8 were pain-free. Exclusions were psychiatric or neurologic disorders (either central or peripheral), substance abuse, opioid use, or diabetes mellitus.

Methods—All participants underwent structural brain magnetic resonance imaging, and all participants with CLBP underwent the 4-m walk test.

Main Outcome Measurements—All the participants were assessed for both global and regional WMH by using an automated localization and segmentation method, and gait speed of participants with CLBP.

Results—The disabled group demonstrated statistically significant regional WMH in a number of left hemispheric tracts: anterior thalamic radiation ($P = .0391$), lower cingulate ($P = .0336$), inferior longitudinal fasciculus ($P = .0367$), superior longitudinal fasciculus ($P = .0011$), and the superior longitudinal fasciculus branch to the temporal lobe ($P = .0072$). Also, there was a statistically significant negative association ($r_s = -0.57$; $P = .0225$) between the left lower cingulate WMH and the gait speed in all the participants with CLBP. There was a statistical difference in global WMH burden ($P = .0014$) and nearly all regional tracts (both left and right hemispheres) when comparing CLBP with pain-free participants.

Conclusions—Our findings suggest that WMH is associated with, and hence, may be accelerated by chronic pain manifesting as perceived disability, given the self-reported disabled

CLBP patients had the greatest burden, and the pain free the least, and manifesting as measurable disability, given increasing WMH was associated with decreasing gait speed in all chronic pain participants.

INTRODUCTION

Disability is a major public health problem that affects more than one-third of older Americans [1]. An increasing body of literature describes a robust relationship in older adults between brain structural abnormalities, predominantly white matter (WM) hyperintensities (WMH), and mobility dysfunction [2–7] as well as disability risk [8–10]. Although age has been identified as the most prominent predictor of WMH burden [11], along with a number of cardiovascular risk factors, particularly diastolic hypertension [12–16], no study that explored the relationship between WMH burden (the total or degree of WMHs) and disability has evaluated the contribution of pain status. At least 50% of community-dwelling older adults experience a chronic nonmalignant pain disorder in which chronic low back pain (CLBP) is one of the most commonly reported [17–18,19]. Although CLBP is associated with self-reported disability in community-dwelling older adults, a number of these studies have failed to demonstrate a relationship between CLBP and observed physical performance, and pain severity is only modestly associated with self-reported disability [20–25]. The mechanistic link between CLBP and disability in older adults is not well understood. Structural brain imaging has been described as a “window” into understanding chronic pain [26]. Structural magnetic resonance imaging (MRI) may also be a window into understanding chronic pain–related disability.

Recent findings from our laboratory demonstrate a significant relationship between brain structural differences and chronic nonmalignant pain in older adults. In our first MRI study [17], we compared brain structure (by using voxel-based morphometry) in older adults with CLBP with individuals who were pain free. We found that participants with CLBP had smaller regional brain volumes (left superior parietal lobe gray matter and middle cingulate WM). Of note, there was no difference in comorbidities, physical performance measures, or neuropsychological testing between the CLBP and pain-free groups.

In our second MRI study [18], we compared brain structure (by using diffusion tensor imaging) and function (by using resting-state functional MRI) in older adults with self-reported disabling CLBP with those with nondisabling CLBP. Similarly, there was no difference in comorbidities, gait speed, or other physical performance measures between the groups, yet one group described themselves as disabled. The disabled group demonstrated significantly lower WM integrity ($P < .05$) of the splenium of the corpus callosum. This group also demonstrated activation of the right medial prefrontal cortex at rest, whereas the nondisabled group demonstrated activation of the left lateral prefrontal cortex. We proposed that activation of the right medial prefrontal cortex in the disabled group may inhibit the supplementary motor area and motor initiation, thus contributing to disability perception. Our theory was based on another study that found the activation of the medial prefrontal cortex takes place with negative autobiographical thoughts (such as “I am disabled”), concomitantly suppressing the supplementary motor area and other motor regions [18,27]. The supplementary motor area is particularly important for the initiation of motor activity,

real or imagined [27–36]. After combining groups, we also found, in our second study, that lower WM integrity was associated with pain duration and poor physical function across all the participants.

Although the cause for the brain structural or functional differences that we found cannot be explained by our research, collectively, our findings established in older adults an important relationship between chronic nonmalignant pain with brain structure and function. More importantly, we demonstrated that the only measurable difference between self-reported participants with CLBP who were disabled and those with CLBP who were not disabled was brain structure and function, which indicated that disability may not necessarily arise from a peripheral physical impediment but from differences in the brain. Given our findings and given the association of WMH with disability and disability risk, we questioned whether there is a difference in WMH between older adults with CLBP who were disabled and older adults with CLBP who were not disabled.

The primary aims of this study were to (1) explore differences in global and regional WMHs between older adults with self-reported disabling CLBP and those with nondisabling CLBP, and (2) examine the association between WMH burden and gait speed by combining all the participants with CLBP (both disabled and nondisabled). The secondary aim was to compare global and regional WMHs of all the participants with CLBP with pain-free controls. With respect to the primary aims, our hypothesis is that the disabled group would demonstrate greater WMH burden than the nondisabled and that WMH burden in all the participants with CLBP would correlate with gait speed deficit. With respect to the secondary aim, our hypothesis is that the subjects with CLBP overall would carry a greater WMH burden than the pain-free controls.

METHODS

Participants

A total of 24 healthy, cognitively intact, community-dwelling older adults (age ≥ 65 years) were studied. The participants with CLBP (n = 16) were recruited from the Pittsburgh Claude D. Pepper Older Americans Independence Center registry. This research was approved by the University of Pittsburgh Internal Review Board, and written informed consent was obtained at the time of enrollment for the subjects with CLBP. The pain-free controls (n = 8) were randomly selected through a chart review from the Healthy Brain Project (HBP), an ancillary investigation to the Health, Aging, and Body Composition (Health ABC) study [25,37]. Health ABC commenced in 1997 and enrolled 3075 black and white men and women aged 70–79 years, in roughly equal numbers. All the participants were free of reported difficulty walking a fourth of a mile, climbing 1 flight of stairs, and performing basic activities of daily living; they resided in the community in designated ZIP code areas that surround the University of Pittsburgh or the University of Tennessee, Memphis, Tennessee. Participants from the HBP were identified at the 10-year examination of Health ABC from the University of Pittsburgh site and had to be able to walk 20 m unaided and meet eligibility criteria for, and agree to receive, an MRI of the brain. The brain MRI scanners and protocols for image collection and analysis are identical to those used for participants with CLBP (described below). For the pain-free controls, permission was

granted by the Health ABC board to access the HBP data, and the HBP study also was approved by the University of Pittsburgh Internal Review Board where written informed consent was obtained from participants at the time of enrollment to allow for data sharing.

The selection process and criteria for the participants with CLBP (Figure 1) are described in detail elsewhere [18]. Briefly, participants were included who reported CLBP every day or almost every day for 3 months of at least moderate intensity. Moderate or greater intensity CLBP was required for study inclusion based on evidence from a large epidemiologic study that demonstrated that older adults with moderate or greater low back pain are significantly more likely to report functional impairment than older adults with less severe pain [25]. Participants were categorized into 2 groups: CLBP self-reported as (1) disabling (pain that necessitated cutting back on daily activities or resulted in being bed bound during some days for >6 weeks over the past 6 months), or (2) nondisabling (pain that had limited function for <6 weeks over the past 6 months). We operationally defined disabling versus nondisabling CLBP by drawing upon the findings of Reid et al [38]. Candidates were excluded if they reported pain (including radiculopathic pain) experienced outside of the lower back of the same or greater intensity or of the same or greater frequency. Exclusions also included a history of, or currently experiencing, a disorder with known effects on brain structure (such as diabetes mellitus [39], depression [40], anxiety [41,42], posttraumatic stress disorder [43], multiple sclerosis, cerebral tumor, traumatic brain injury, dementia, or a cerebrovascular accident) or brain function (such as substance abuse and seizure disorder). Exclusion also resulted if a candidate reported taking or had taken in the past 3 months prescription and over-the-counter psychotropics, scored <24 on the Folstein Mini-Mental State Examination [44,45], or was mobility impaired (Parkinson disease, foot drop, radicular symptoms that interfered with testing, or unable to ambulate without a walker or care) so as not to confound gait speed assessment. Finally, participants were excluded if they were experiencing an acute illness or had conditions that would render MRI unsafe. Of the 168 older adults screened by using telephone calls, 36 were deemed eligible for onsite evaluation, and 16 were enrolled and completed the study. Common reasons for exclusion were ineligible pain status (ie, CLBP not experienced every day or almost every day, CLBP of less than moderate intensity, or pain outside of the back greater than the CLBP) and diabetes mellitus.

For the pain-free controls, the same exclusion criteria were applied during a chart review of 100 randomly selected files from the HBP hard copy files (Figure 1). At the time of the HBP chart review, 344 participants had been enrolled. Selection criteria for the controls were applied to assessments, and data collection was performed and recorded within 1 year before MRI data collection. If no assessments or data were recorded within 1 year of the MRI, then the person was excluded. For inclusion as a pain-free control, a strict definition of pain-free was applied: answering no to all pain status assessments and no documentation of analgesic use during the prior year, including psychotropics (eg, antidepressants, antipsychotics, aspirin, fish oil). Cognitively intact was defined as a score of >77 on the Modified Mini-Mental State Examination [46,47]. The Mini-Mental State Examination and Modified Mini-Mental State Examination have been found to be equivalent in screening for dementia [47]. Of the 100 randomly selected files, 94 charts were reviewed, and 8 persons were deemed eligible for inclusion based on the criteria described above. Common reasons for exclusion were similar to those for subjects with CLBP: ineligible pain status (in this case, reporting

pain or records that indicated potential pain management) and diabetes mellitus. Another important reason for exclusion was the lack of assessments or data recorded within 1 year of the WMH MRI.

Imaging Methods and Analysis

All brain images for participants with CLBP and pain-free controls were acquired at the University of Pittsburgh's Magnetic Resonance Research Center by using a Siemens 3T Total Imaging Matrix TRIO scanner (Siemens Medical Solutions USA Inc, Malvern, PA). Each scanning session began with 3-dimensional magnetization-prepared rapid gradient-echo high-resolution T1-weighted image acquisition for anatomic detail (matrix, 256×256 ; repetition time, 2300 ms; echo time, 3.43 ms; field of view, 25; axial slices, 160; thickness, 1.0 mm; and flip, 9) and for extracting WMH burden, fluid attenuated inversion recovery T2-weighted images were collected (matrix, 256×256 ; repetition time, 9160 ms; echo time, 89 ms; field of view, 256 mm; inversion time, 2500; 3-mm axial slices; number of excitations [NEX], 1, with interleaved acquisition to calculate WMH volume).

An automated WMH localization and segmentation method [48,49] was used to compute normalized WMH volumes globally and in 20 standardized tracts identified by the Johns Hopkins White Matter Atlas [50], including association, projection, and commissural fibers (see Table 1 for complete list). The calculated WMH volumes were normalized for the overall brain volume. The automated WMH segmentation method is an iterative algorithm that involves automated selection of seeds of possible WMH lesions and by using fuzzy connectedness to segment WMH lesions around the seeds. A detailed and precise mathematic definition is given in Udupa and Samarasekera [49]. The fully automated WMH segmentation system was implemented in C++ and Insight Segmentation and Registration Toolkit (Insight Software Consortium, Chapel Hill, NC). The WMH matter extraction algorithm is available upon request (<http://www.gpn.pitt.edu>) and has been implemented by more than 30 neuroimaging researchers.

Additional Data Collection, Including Gait Speed Assessment

For all the participants, the additional following information was collected on-site: demographics (including age, ethnicity, gender, economic, and educational status); pain status; and documentation of all regularly scheduled and as needed prescription medications plus over-the-counter medications, including vitamins, supplements, herbals, and herbal teas. Pain intensity was assessed in the participants with CLBP by using McGill Pain Questionnaire Short Form [51] and comorbidities by using the Cumulative Illness Rating Scale (CIRS) [52,53]. HBP did not collect CIRS scores but, instead, extensively documented the medical health of all the participants. Gait speed, a reliable and valid measure of current and future disability [54–56] was assessed (4-m walk for the subjects with CLBP and 6-m walk for the pain-free controls). The 4-m and 6-m walks were normalized to a m/s value.

Statistical Analysis

Analysis of variance was used to assess age differences among the 3 groups. The Fisher exact test was used for between-group comparisons of categorical data, including ethnicity, gender, income, and education. The Student *t*-test was used to compare CIRS scores

between the disabled and nondisabled groups. For between-group comparison of continuous measures, WMH values and gait speed, analysis of covariance was applied by using age as a covariant. For association analysis of WMH and gait speed of the subjects with CLBP, the Spearman correlation coefficient was used with a P value $< .05$ deemed significant and no correction for multiple comparisons.

RESULTS

Participant Characteristics

Participant characteristics are shown in Table 1. There was no significant difference in age between the disabled ($n = 8$; mean age, 74.1 years) and the nondisabled group ($n = 8$; mean age, 75.1 years); however, the pain-free controls were significantly older than the subjects with CLBP (hence, age was controlled for throughout the analysis). There was no difference among the 3 groups in ethnicity, gender, income, education, or prevalence of hypertension. In addition, there was no difference in CIRS scores or total months of everyday CLBP between the disabled and nondisabled groups. HBP did not collect CIRS scores but, instead, extensively documented the medical health of the participants. A review of these histories indicated that the selected pain-free cohort was as medically healthy as the subjects with CLBP. Overall, the participants were healthy and took few medications, with the exception of multivitamins and over-the-counter supplements. Given the small sample size, the heterogeneity of the over-the-counter supplements, and the fact that prescription pharmaceutical use was rare, medication data were not further analyzed.

WMH

As illustrated in Table 2 and Figure 2, the disabled group compared with the nondisabled group demonstrated statistically significant regional WMH burden in a number of left hemispheric tracts (anterior thalamic radiation) ($P = .0391$), lower cingulate ($P = .0336$), inferior longitudinal fasciculus ($P = .0367$), the entire superior longitudinal fasciculus ($P = .0011$), and the superior longitudinal fasciculus branch to the temporal lobe ($P = .0072$), with a nonsignificant trend toward greater global WMH burden ($P = .0635$). When comparing all 3 groups, there was a statistical difference in overall global WMH burden ($P = .0014$) and in nearly all 20 tracts, both left and right hemispheres (see Table 1 for details). In a subanalysis, pairwise comparison of the disabled and nondisabled groups with the control group indicated that the disabled group carried the greater WMH burden (disabled $>$ nondisabled $>$ controls); in the disabled group, more tracts were affected. Further, the WMH burden was significantly greater in the tracts of the participants who were disabled, with the exception of the right corticospinal tract.

Gait Speed

Pairwise analysis revealed no statistical difference ($P = .7865$) in gait speed between the participants with CLBP who were disabled and participants with CLBP who were not disabled, and, overall, there was no statistical difference in gait speed among the 3 groups ($P = .1116$).

WMH and Gait Speed

For participants with CLBP overall, there was a statistically significant negative association ($r_s = -0.57$; $P = .0225$) between left lower cingulate WMH and gait speed.

DISCUSSION

To our knowledge, this is the first study to explore WMH burden in older adults with self-reported nondisabling and disabling CLBP and to compare the WMH burden in older adults with pain with those who were pain-free. With respect to the primary aim, the group with disabling CLBP demonstrated a higher WMH burden lateralized to the left hemisphere tracts compared with the group with nondisabling pain. After combining the CLBP groups (disabling and nondisabling), higher WMH burden in the left lower cingulate was associated with slower gait speed. With respect to the secondary aim, there was an overall greater WMH burden in those with pain compared with the pain-free controls. Of relevance, both the subjects with CLBP and the pain-free controls were relatively free of WMH-associated cardiovascular risk factors [12–16] and were balanced with respect to prevalence of hypertension. Thus, the differences in WMH were very likely related to pain. As important, although we controlled for age, the pain-free cohort was older, which lent further support to pain being an independent contributor to WMH burden.

Although there was no difference in gait speed between the disabled and nondisabled groups, there were significant differences in WMH burden between the 2 groups with left lateralization of the WMHs (see Table 1 and Figure 2). Functional MRI studies have found that imagery of a motor activity as well as imagining a motor activity, such as walking, will activate the same regions of the brain involved in execution of motor activity, particularly earlier stages of motor control [30–36,57,59,60]. There is evidence that indicates that being able to imagine a motor activity such as walking may be a necessary element of motor control [31,58], notably gait initiation [58]. The cortices that share motor imagery, planning, and execution, such as the supplementary motor area, the primary motor cortex, the dorsolateral prefrontal cortex, the superior and inferior parietal cortex [32,57,60], rely upon projection and association tracts such as the lower cingulum [61,62], superior longitudinal fasciculus, and the superior longitudinal fasciculus branch to the temporal lobe [61–63]. If cortical connections are necessary to integrate the actions of imagining and executing a motor task, then perceived mobility disability might begin with an inability to integrate imagining the action with its execution, even though the action, that is, walking, may not significantly differ once executed. However, it is possible that, with increasing loss of association, projection, and commissural fibers, the action of walking would deteriorate as well, which may explain the significant relationship between increased WMH burden of the left lower cingulum with decreased gait speed after combining groups (disabled and nondisabled). Similarly, when we combined groups (disabled and nondisabled) in our previous study, we found a significant relationship between gait speed and the left centrum semiovale (which houses most of the left-sided tracts assessed in the current study, such as the cingulum) in which poorer WM integrity was associated with decreased gait speed [18]. The 2 studies together corroborate an association of left lateralization of brain WM structural deficits with poorer gait mobility. Given that an association of gait speed as well

as other assessments of gait have been consistently associated with WM deficits [2–7,64] and disability risk [8–10], further investigation of the contribution of chronic pain to mobility disability is warranted.

Only one other study has looked at WMHs in older adults (n=49; mean age, 72.4 years) with chronic pain (principally arthritis) [65]. Oosterman et al [65] examined the relationship between WMHs and pain intensity (by using the color analog scale) as well as pain affect (by using a verbal rating scale from the McGill Pain Questionnaire, the Number of Words Chosen-Affective). WMH burden was significantly related to pain affect but not to intensity, with lateral periventricular WMHs the strongest predictor of pain affect; hence, the greater the WMH burden, the greater the severity of the affective pain descriptors. Although depressive symptoms were controlled for, confounding the study was inclusion of the participants with comorbidities that are known to impact brain structure (eg, diabetes, hypertension, and significant heart disease). Despite the limits on the findings by Oosterman et al [65], the dissociation of pain intensity and pain affect in relation to WMH burden may be important. In our own study, we required the same level of pain intensity for both participants who were disabled and participants who were not disabled so to avoid pain severity independently influencing brain structure and function. The only difference between the participants with CLBP was the self-reporting of disability, hence, an affective element of chronic pain. Our findings in the context of the study by Oosterman et al [65] further highlight that WMH burden may impact how the brain integrates and functions with respect to the affective element of chronic pain, perhaps leading to perceived disability (and as we suggested above, possibly manifest disability). However, given the cross-sectional nature of the study by Oosterman et al [65] and our study, causality cannot be established.

An important question is whether chronic pain is changing brain structure and function. This is particularly important when one looks at our current findings, which demonstrate that the younger subjects with CLBP carry a greater WMH burden than the pain-free subjects in the absence of other comorbidities that negatively impact brain structure. The subjects in the pain-free cohort were older, which lends further support to pain as an independent contributor to WMH. With this in mind, another question is whether the impact of chronic pain on brain structure is an acceleration of aging, thus contributing to disability.

A recently published 4-year longitudinal study [66] of 99 healthy community-dwelling older adults (mean [standard deviation] age, 82.1 ± 4.1 years) found that the total WMH burden was as reliable as regional WMH in predicting functional decline in measured mobility, cognition, and reported urinary continence. The investigators suggested that seemingly distinct geriatric syndromes that result in functional impairment may share a common risk factor, WMH burden, and that WMH burden could be a useful marker for predicting disability. Of note, pain status was not assessed and the extent of cardiovascular disease in the study's participants was uncertain. If the participants (described as healthy) were relatively free of cardiovascular disease, then a possible etiologic factor could be chronic nonmalignant pain, which further emphasizes the need to understand the longitudinal impact of chronic pain on brain structure and function in older adults.

This study's limitations should be noted. We could statistically demonstrate that the subjects with CLBP did not differ with respect to comorbidities and that hypertension did not statistically vary with all of the groups. However, HBP did not collect comprehensive data on medical or psychiatric comorbidity; therefore, comorbidities of the pain-free participants could not be assessed statistically. Nonetheless, inclusion in the parent Health ABC study as well as the HBP was predicated on participants being in good health; chart review confirmed that the subjects remained in good health. In addition, the same psychoneurologic exclusions were applied to the HBP study as to our own, thus, the possibility of comorbidities confounding our results would be minimal. Given that the pain-free controls were selected from a different study, we cannot assure cross-study reliability in measurements, for example, gait speed; however, we are confident that the HBP study was internally consistent and reliable in its measurements. (As stated above, WMH data were collected in the same manner and were analyzed in the same laboratory with the same standardized and validated paradigms.) Due to the number of assessments, the possibility of spurious results cannot be ruled out. Corrected *P* values in this exploratory study were not used, because it was deemed that the cost of missing a finding outweighed the value of using corrected *P* values. Finally, there are a number of factors not explored in this study that could have impacted WMH burden, such as sleep, nutrition, stress, and remote physical or psychological traumas.

CONCLUSION

A growing body of research has substantiated a relationship between chronic pain and brain reorganization [26]. In older adults, restoration of gray matter has been observed after treatment of chronic pain, notably hip osteoarthritis [67,68]. Our research further corroborates that brain structure may be susceptible to chronic pain, which may then contribute to disability or disability risk. Given that WMHs are associated with nonspecific pathologic damage to WM [69–71] and have been associated with a number of geriatric syndromes [66,72] and disability risk [8–10,73], it is important to understand the impact of chronic pain on brain structure and function in older adults. Neuroplasticity is not only about deficits that arise in the brain but also about changing brain structure and function in a positive manner. We demonstrated that mindfulness meditation in older adults with CLBP decreases self-reported functional limitation [74], and it has been found studies that meditation not only modulates pain processing [75] but changes brain structure, such as increasing cortical thickness [76]. In addition, mental imagery and mental practice of an action (commonly used by elite athletes) has been used to support rehabilitation of motor deficits in a variety of neurologic disorders in nonathletes [77,78], including stroke [79,80] and balance in elderly women [81]. As we look for those factors that negatively impact brain structure and/or function that leads to disability, such as chronic pain, it is equally important to investigate and institute those practices that prevent deficits and, hence, disability. In an aging population, multimodality nonpharmacologic treatment of pain is a clinical imperative. If we understand the nature of brain structural and functional changes, then we can better target treatments that perhaps prevent if not reverse these changes, thereby preventing or reversing disability.

Acknowledgments

We thank the HBP (funded under grant R01AG029232 by the National Institute on Aging [NIA]) and the Health ABC study (funded under N01-AG-6-2106, N01-AG-6-2103, and N01-AG-6-2106 by NIA contracts, as well as NIA grant R01-AG028050, and National Institute of Nursing Research grant R01-NR012459) for access to their data and their overall support with special thanks to Anne Newman, Tamara Harris, Gregory Hicks, Steve Kritchvsky, and Kristine Yaffe. We also thank the following people for their generous assistance and hard work in completing this study: Denise Davis at the University of Pittsburgh Medical Center, Presbyterian MR Research Center, and R. P. Detwiler. We thank Stephanie Studenski for sponsoring Neilly Buckalew under a National Institutes of Health T32 Predoc and Postdoc Training grant from the NIA and Amber Barnato of the Clinical Scientist Training Program and Michael Boninger of the Department of Physical Medicine and Rehabilitation for their added mentorship. We also extend our gratitude to the NIA for funding N. Buckalew's training as well as to Arthur Levine, senior vice chancellor for the Health Sciences and dean of the School of Medicine at the University of Pittsburgh. This work was also supported by a grant from the University of Pittsburgh's Claude Pepper Older Americans Independence Center and in part by the Intramural Research Program of the National Institutes of Health, NIA.

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CME Question

In which of the following hemispheric tracts was a statistically significant ($P < .05$) difference found in the regional white matter hyperintensity (WMH) burden when comparing participants with disabling versus nondisabling chronic low back pain?

- a. left superior longitudinal fasciculus
- b. left uncinate fasciculus
- c. right corticospinal tract
- d. right upper cingulate

Answer online at me.aapmr.org

Figure 1.
Screening and enrollment process.

Figure 2.

Left hemisphere tracts with statistically significant greater white matter hyperintensities (WMH) burden demonstrated by participants with chronic low back pain (CLBP) and with disabling pain compared with nondisabling pain, including the anterior thalamic radiation (ATR-L) ($P = .0391$), lower cingulate (CgL-L) ($P = .0336$), the superior longitudinal fasciculus (SLF-L) ($P = .0011$), including the SLF branch to the temporal lobe (SLFBT-L)

($P = .0072$), and the inferior longitudinal fasciculus (ILF-L) ($P = .0367$). Anterior is at the bottom of the figure and posterior at the top of the figure.

Table 1

Participant characteristics

Variable	Disabling (n = 8)	Nondisabling (n = 8)	Control Subjects (n = 8)	P Value
Age, mean (SD)	74.1 (6.4)	75.1 (7.3)	82.3 (1.7)	.02*
Ethnicity (white/black/Hispanic)	7/1/0	5/3/0	6/2/0	.60 [†]
Gender (female/male)	4/4	2/6	4/4	.66 [†]
Income (<\$50K/>\$50K)	5/3	5/3	2/6	.38 [‡]
Education, years, n				.64 [‡]
<12	0	2	2	
12	1	0	1	
>12	7	6	5	
Hypertension, n	2	1	3	.83 [‡]
Total months everyday CLBP, median (IQR)	84 (7–420)	102 (4–180)	—	.95 [‡]
CIRS	22 (2.1)	22 (4.1)	—	.60 [‡]

CLBP = chronic low back pain; IQR = interquartile range; CIRS = Cumulative Illness Rating Scale.

* Analysis of variance.

[†] Fisher exact test.

[‡] Wilcoxon Rank-Sum.

Table 2

Age adjusted pair-wise and overall statistical comparisons of white matter hyperintensity values*

Variable	Disabling and Nondisabling (P > F)	Nondisabling and Controls (P > F)	Disabling and Controls (P > F)	Overall (P S > F)
Global	.0635	.0127 [†]	.0003 [†]	.0014 [†]
Frontal corpus callosum	.2023	.0109 [†]	.0010 [†]	.0037 [†]
Occipital corpus callosum	.2394	.0009 [†]	.0001 [†]	.0004 [†]
L anterior thalamic radiation	.0391 [†]	.0023 [†]	.0001 [†]	.0169 [†]
L corticospinal tract	.2157	.5015	.0957	.2138
L lower cingulate	.0336 [†]	.0148 [†]	.0002 [†]	.0009 [†]
L upper cingulate	.0535	.1321	.0039 [†]	.0124 [†]
L interior fronto-occipital fasciculus	.1150	.0027 [†]	.0001 [†]	.0005 [†]
L inferior longitudinal fasciculus	.0367 [†]	.0159 [†]	.0002 [†]	.0010 [†]
L entire SLF	.0011 [†]	.2675	.0003 [†]	.0005 [†]
L SLF branch to the temporal lobe	.0072 [†]	.6476	.0072 [†]	.0084 [†]
L uncinate fasciculus	.8812	.2169	.2827	.4266
R anterior thalamic radiation	.0916	.1036	.0050 [†]	.0169 [†]
R corticospinal tract	.8543	.0268 [†]	.0438 [†]	.0620
R lower cingulate	.3135	.0937	.4201	.2239
R upper cingulate	.7103	.3738	.2442	.4897
R interior fronto-occipital fasciculus	.4217	.0497 [†]	.0133 [†]	.0396 [†]
R inferior longitudinal fasciculus	.5488	.0132	.0051	.0132 [†]
R entire SLF	.1415	.1597	.0134 [†]	.0421 [†]
R SLF branch to the temporal lobe	.0910	.3547	.0249 [†]	.0617
R uncinate fasciculus	.7025	.9088	.6637	.8887

F = F statistic; L = left; R = right; SLF = superior longitudinal fasciculus.

* Using analysis of covariance. The group with the greater white matter hyperintensity volume in the pair-wise comparisons is listed first.

[†] Statistically significant.