

Cerebellar white matter volume and clinical pain in older individuals

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Abstract: Recent work shows that white matter (WM) significantly contributes to the detrimental effects of chronic pain on mobility in community-dwelling older adults (Cruz-Almeida et al., 2017). The cerebellum specifically plays a key role both in motor and pain processing (Moulton et al., 2010). The aim of the present study was to determine the associations between WM volumes in the cerebellum and chronic pain intensity and disability in older individuals. **Methods:** Participants (n=39) over 60 years of age enrolled in the Neuromodulatory Examination of Pain and Mobility Across the Lifespan (NEPAL) study, filled out the Graded Chronic Pain Scale (GCPS) to assess characteristic pain intensity and pain disability during the past six months and underwent a structural MRI scan. Freesurfer's recon-all function was used to determine cerebellar WM volumes. Subcortical segmentation (aseg) statistics were extracted and statistical analyses were conducted with Rstudio. **Results:** Given the large differences in cerebellar WM volume between males (n=9) and females (n=30), and the small sample size of male participants, associations were further examined specifically within the female sample. GCPS Characteristic Pain Intensity was negatively correlated with WM volume in the cerebellum ($r = -0.39$, $df = 36$, $p\text{-value} = 0.01435$), but no associations were detected with GCPS Pain Disability. **Conclusion:** The finding that lower WM volume in the cerebellum was associated with higher self-reported chronic pain intensity, but not pain disability, may be explained by the cerebellum's involvement in somatosensory and pain perception and processing that are likely to become dysregulated with age and chronic pain.

Introduction

Chronic pain is reported to be the most prevalent and expensive public health condition in the United States, affecting 100 million people in the United States, with about a \$635 billion annual cost to society (Gereau et al., 2014). While chronic pain affects individuals of all ages, races, and genders, it disproportionately impacts older adults. Along with its significant societal burden, chronic pain in older adults is associated with substantial disability from reduced physical function (Mansour et al., 2013). The lack of successful treatment options to target chronic pain is the result of incomplete understanding of the underlying, neurobiological mechanisms involved across different populations who experience chronic pain. Gender and demographic differences exist within the older population, especially in populations of individuals with co-morbidities and cognitive impairments who are often undertreated for pain (“Relieving Pain in America,” 2011). Musculoskeletal pain is highly prevalent in the older, community-dwelling population and severely limits physical function including mobility (Wilkie et al., 2007). Bothersome pain in the last month was reported by half of the older, community-dwelling adult population in the United States and was strongly associated with lower physical function (Patel et. al, 2013). This limitation on mobility and ability to participate in activities negatively impacts quality of life.

Definition and Neurobiology of Pain

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” Pain is a multidimensional experience with sensory, affective and cognitive-evaluative components, each of which interacts and contributes to the final highly individualized pain experience (Melzack and Casey, 1968). As treatments should not be initiated without proper assessment, measuring pain is the first, critical step of pain management. Chronological age also impacts the dimensions of pain, and therefore, the assessment and treatment of pain in the elderly population, requires a holistic approach (Gagliese and Melzack, 1997). Since pain is a subjective, cognitive percept, self-report measures are widely used and are the gold standard to quantify it. Thus, the multidimensional pain experience can be studied as a perception requiring the involvement of a widespread and distributed number of brain regions and their interactions. In acute pain, noxious stimuli are transduced to the dorsal horn of the

spinal cord where a variety of transmitters signal the brain through spinal neurons via various ascending pathways. The acute pain signal reaches the primary and secondary somatosensory, insular, cingulate, prefrontal as well as limbic brain regions. Conversion to chronic pain may be promoted by dysfunction in descending pain modulatory circuits and exogenous factors arising from higher structures that govern emotional and cognitive processes (Ossipov et al., 2014).

Neuroimaging studies in persons with chronic pain demonstrate distinct brain activity and morphological brain alterations (Apkarian et al., 2005, 2009, 2011). Studies also show partial reversal of brain morphology with treatments that reduce the burden of chronic pain (Seminowicz et al., 2011). White matter (WM) structure in the brain has been implicated in recent literature related to chronic pain and aging, and in transition from acute to chronic pain (Mansour et al. 2013). Chronic pain can contribute to white matter structure change, and therefore, to disability in older adults, suggesting that changes in white matter structure predict transition to chronic pain and reduced mobility.

In the paper by Sullivan and colleagues (2001) regional differences in white matter microstructural intravoxel coherence, and macrostructural intervoxel coherence, were measured. According to the study, age-related decline in white matter microstructure was equally strong and similar in both men and women, with greater age-dependent deterioration in frontal rather than parietal regions (Sullivan et al., 2001). This is consistent with other studies indicating that areas associated with cognition, processing speed, and memory are more likely to undergo age-related decline. While the study indicated that large-scale, macrostructural intervoxel coherence did not change significantly with age, this could be because WM microstructure becomes less packed with age, where axonal fibers are macrostructurally oriented similarly in neighboring voxels, maintaining a false sense of white matter integrity. For this reason, studies also include WM volume and white matter hyperintensity (WMH) as measures of WM structure.

In addition to research focused on the brain's WM microstructure (i.e. fractional anisotropy) in normal aging unmarked by lesions, recent studies have integrated chronic pain into the relationship between WM structure and aging. A study conducted at the University of Pittsburgh first reported significantly lower white matter volume in older adults with chronic low

back pain compared to older adults without chronic low back pain (Buckalew et al., 2008). Their results also showed that disabled participants with chronic pain had statistically significant regional WMH burden (Buckalew et al., 2013). Although these studies had small sample sizes of sixteen and twenty-four people respectively, results suggest that WMH could be accelerated by chronic pain manifesting as perceived disability because increased WMH was associated with decreased gait speed in all chronic pain participants.

Furthermore, recent research specifically implicates white matter (WM) integrity, both macro- and microstructural, in contributing to the detrimental effects of musculoskeletal pain on mobility in community-dwelling, older adults (Cruz-Almeida et al., 2017). In this study, cerebral mechanisms were explored as a potential mediator between musculoskeletal pain and physical performance. This provides neuroimaging evidence that lower integrity of the brain's WM, specifically macrostructural WMH and microstructural WM fractional anisotropy (FA), significantly mediates the relationship between pain and mobility in high functioning, community-dwelling older adults.

Pain and the Cerebellum

Certain regions of the brain have been identified as key players in pain pathways and modulation. While the cerebellum has classically been considered as an important region for motor processing, and it is also believed to play a role in non-motor, higher cognitive processes (Schmahmann, 1991). More recently, the cerebellum has been implicated in somatosensory processing including nociception (Saab et al., 2003). Afferent input from nociceptors reaches the cerebellum through two different and segregated pathways, the spino-ponto-cerebellar and the spino-olivo-cerebellar path (Ekerot et al., 1987). Both animal and human research indicates that primary afferents conduct nociceptive input to the cerebellum and that electrical and pharmacological stimulation of the cerebellum can modulate nociceptive processing. Furthermore, increased cerebellar activity has been associated with acute and chronic pain (Moulton et al., 2010). Encoding of nociceptive information after it reaches the cerebellum remains unclear. The cerebellar influence on pain processing, however, is believed to be inhibitory on the primary motor cortex due to Purkinje cells, with a recent study in monkeys describing this mechanism as cerebellum-brain inhibition (Kelly and Strick, 2003).

Neuroimaging studies with human subjects have specifically revealed pain intensity-related activation that occurs bilaterally in the cerebellum (Coghill et al., 1999). Another neuroimaging study showed evidence that nociceptive-specific activation is processed in the deep cerebellar nuclei, anterior vermis, and bilaterally in cerebellar hemispheric lobule VI (Helmchen et al., 2003). While this was the first study to explicitly associate activity in the cerebellum with human pain perception, a follow-up paper published a year later showed contrasting evidence, as cerebellar activity varied with pain ratings only when the noxious stimuli were self-administered by the subjects being scanned, and this was no longer the case when pain was applied by experimenters (Helmchen et al., 2004). The discrepancy between results was not explained and details about how nociceptive information is encoded once it reaches the cerebellum is lacking (Moulton et al., 2010). Thus, the cerebellum's capacity for nociceptive encoding needs to be further explored in both humans and animal models.

Additionally, structural cerebellar changes related to aging with pain remain understudied. While it has been shown that the cerebellum at the molecular level ages slower than other human brain tissues (Horvath et al., 2015), specific cerebellar changes with age have been observed recently, showing decline with age in total cerebellar volume, global cerebellar white matter volume, and mean volume of Purkinje cell body (Andersen et al., 2003). Furthermore, gender differences in gross cerebellar neuroanatomy have been recorded by many studies, particularly in the vermis region, with differential hemispheric cerebellar volume observed in men and women (Raz et al., 1998).

While cerebellar pain pathways have been studied recently, relationships between changes in cerebellar white matter structure and chronic pain in the aging population are understudied. Understanding this relationship could pave the way for successful pain management to improve both mobility function and brain health. Therefore, the aim of the present study was to determine the associations between self-reported pain, both intensity and disability, and cerebellar WM volumes in older adults. Given previous evidence of whole-brain WM structure decline in older individuals with chronic pain, we hypothesized a negative correlation between WM volume, specifically in the cerebellar region, with clinical pain intensity and disability.

Methods

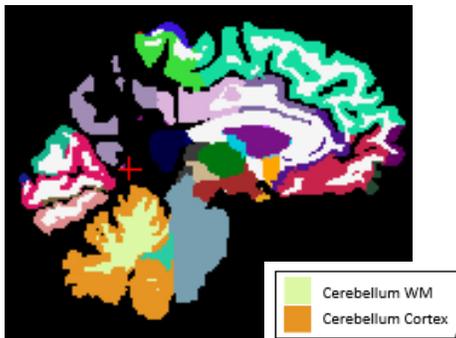
Participants (n=39) over 60 years of age, enrolled in the Neuromodulatory Examination of Pain and Mobility Across the Lifespan (NEPAL) study at the University of Florida, filled out the Graded Chronic Pain Scale (GCPS) to assess characteristic clinical pain intensity and pain disability during the past six months (Figure 1) and underwent a structural MRI scan. As part of this study, experimental sessions and neuroimaging were scheduled after successful completion of phone screening to ensure specific MRI eligibility including claustrophobia and presence of any metal in the body. At the first study visit, informed consent was obtained and participants were further screened for major disorders such as depression, bipolar disorder, multiple sclerosis, Alzheimer's disease, uncontrollable high blood pressure, liver or kidney disease, and brain tumors, which are all known to affect brain structure and function. The University of Florida Institutional Review Board (IRB-01) approved the study.

Graded Chronic Pain Scale (GCPS)

GCPS sub-scales were used to determine the chronic pain experience of participants during the past six months. Since chronic pain is a multidimensional phenomenon, pain intensity and pain-related disability are important attributes of any chronic pain condition (von Korff et al., 1992). Characteristic Pain Intensity is a score derived from questions 1-3 with a scale range 0-100, while the disability score is derived from questions 5-7 with the same scale range 0-100. GCPS evaluates global pain severity and pain-related interference with a 0-10 numeric rating scale for each question as shown in figure 1. The three items in each section were averaged and multiplied by 10 to generate both a GCPS characteristic pain intensity and disability score (Cruz-Almeida et al., 2014).

structures from `mri/aseg.mgz` and wrote an output to file `stats/aseg.stats`. WM segmentation was performed to separate WM from the rest of the brain with input `mri/brain.mgz` and output `mri/wm.mgz`. In the last stage of volumetric processing, the mid brain was cut from the cerebrum, and the hemispheres were cut from each other; the left hemisphere was binarized to 255, while the right hemisphere was binarized to 127. All output files were maintained in separate directories for individuals on the University of Florida's HiperGator supercomputing database.

Figure 2: WM segmentation of the brain with Freesurfer 6.0 recon-all function



When Freesurfer crashed without providing an output after repeated attempts, that scan was omitted and noted in results. No manual correction of Freesurfer segmentation was performed. Automated segmentations and parcellations were quality checked using the Freeview utility by a graduate student and myself. Freesurfer also provided an estimated total intracranial volume (eTIV) to check for individual differences in head size, and this value was internally extrapolated from the transform of each brain from native to standard space. Prior investigators have noted the difficulty in determining the best method for normalizing regional volumes, and there is no standard method used for volumetric data (Arndt, et al., 1991). In this study, controlling for eTIV in the linear regression model did not change the significance of results, and it was subsequently excluded from the final statistical model. Using the HiperGator 2.0 supercomputer, scripts were run in parallel for multiple sets of data, with a run-time of about one day for each. Freesurfer's recon-all function was utilized in the present analysis with the following script:

```
$ recon-all -subjid <subject> -i <subject>/T1.nii -all -sd <subject>
```

Next, subcortical segmentation (aseg) statistics were extracted to a text file and then converted to CSV format, allowing for user-friendly import into statistical software packages using the following scripts:

```
$ asegstats2table -i <subject>/stats/aseg.stats --meas volume --tablefile asegstats.txt  
$ sed 's/ \+/,/g' asegstats.txt > asegstats.csv
```

Statistical Analysis

Analyses were conducted on the local workstation with Rstudio. To avoid assigning arbitrary cut-offs for pain and no-pain phenotypes, a linear regression approach was chosen for statistical analysis. Within the Rstudio application, ggplot 2 was used to create scatter plots and display regression lines (Wickham, 2009). The following code was used to create the regression plot:

```
> ggplot(data = <asegstats.csv>, aes(x = GCPS_Characteristic_Pain_Intensity_Score,  
y = Bilateral_Cerebellum_White_Matter, subset = Sex == "<sex>")) +  
geom_point(color='blue') + geom_smooth(method = "lm", se = FALSE)
```

The YaRrr package was used to run Pearson's product-moment correlations between hemispheric cerebellum WM volumes and GCPS subscales (Phillips, 2017). The statistical analysis excluded one female participant and one male participant due to incompatible structural MRI data with Freesurfer software and a missing GCPS score. Associations were examined in a sample size of thirty-seven participants consisting of twenty-nine females and eight males. As there were no significant differences between hemispheric volumes, left and right hemispheric cerebellar WM volumes were added together to obtain a bilateral cerebellar WM volume, and statistical analyses were conducted using the following R script:

```
> cor.test(formula = ~ GCPS_Characteristic_Pain_Intensity_Score +  
Bilateral_Cerebellum_White_Matter, data = <asegstats.csv>)
```

Results

The majority (89%) of participants (mean age of 72 ± 7.8 years) reported chronic pain during the past six months. Given the large differences in cerebellar WM volume between males ($n=9$) and females ($n=30$) and the small sample size of male participants, associations were examined within gender sub-groups after analysis of the full sample. Table 1 shows demographics for the more closely examined, older female sub-group.

Table 1: Demographics for female participants over the age of 60 years

	Total Sample (n=30)		Total Sample (n=30)
Chronological Age, mean \pm SD years	71.13 \pm 5.88	Education, no. (%)	
BMI, mean \pm SD kg/m ²	27.78 \pm 6.16	High school degree	10 (33.33)
Sex, no. (%)		Two-year college degree	6 (20.0)
Female	30 (100)	Four-year college degree	7 (23.33)
Income, no. (%)		Master's degree	5 (16.67)
< \$70,000	17 (60.71)	Doctoral degree	2 (6.67)
> \$70,000	11 (39.29)	Race, no. (%)	
Handedness, no. (%)		Caucasian	29 (96.67)
Right	30 (100)	African American	1 (3.33)

GCPS Characteristic Pain Intensity was negatively correlated with WM volume in both hemispheres of the cerebellum (right hemisphere: $r = -0.41$, $df = 36$, p -value = 0.0112, left hemisphere: $r = -0.37$, $df = 36$, p -value = 0.0203). While the observed negative correlation was stronger in the right hemisphere than in the left hemisphere, both showed a similar trend, and white matter hemispheric volumes were added together and further examined bilaterally.

GCPS Characteristic Pain Intensity was significantly associated with bilateral cerebellar white matter volume ($r = -0.39$, $df = 36$, p -value = 0.01435), while GCPS Pain Disability did not show this trend ($r = -0.11$, $df = 36$, p -value = 0.497). In the subset of females, this negative correlation between pain intensity and cerebellar WM volume was strengthened ($r = -0.50$, $df = 28$, p -value = 0.005769), while the relationship was not observed within the male subset of participants ($r = 0.11$, $df = 7$, p -value = 0.782).

Following the recon-all segmentation and parcellation procedures, two participants were excluded due to an incompatible structural MRI image and a missing GCPS score. The incompatible MRI image failed Freesurfer processing, defined as program failure to produce an output. Figure 3 shows the strong negative correlation for female participants, indicating that lower cerebellar WM volume was significantly associated with higher clinical pain intensity. Figure 4 shows the negative correlation between cerebellar WM volume and clinical pain intensity for all participants. Figure 5 shows three representative figures as seen in the Freeview utility with their corresponding self-report clinical pain intensity scores.

Figure 3: Associations between cerebellar WM volume and clinical pain intensity in older women participants ($r = -0.50$, $df = 28^*$, $p\text{-value} = 0.005769$).

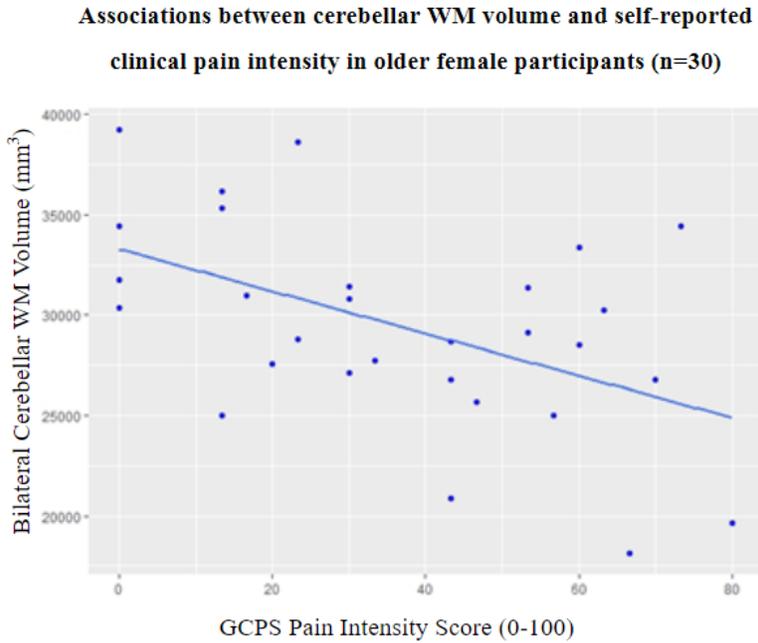
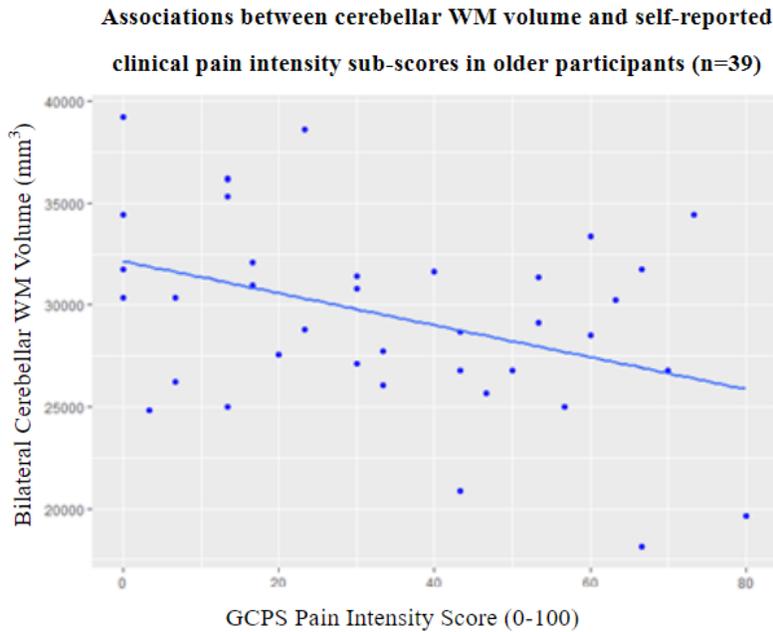
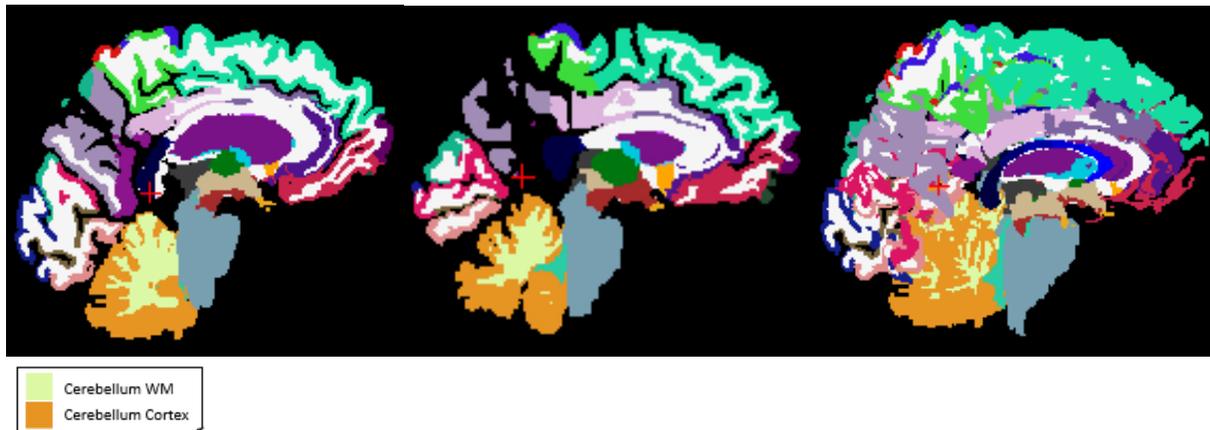


Figure 4: Associations between cerebellar WM volume and clinical pain intensity in older participants ($r = -0.39$, $df = 36^*$, $p\text{-value} = 0.01435$).



*One male was excluded due to incompatible structural MRI data with Freesurfer software and one female was excluded due to a missing GCPS score.

Figure 5: Sagittal slice of cerebellar WM segmentation *in vivo* for participant with GCPS intensity score of 0 (left), sagittal slice of cerebellar WM segmentation *in vivo* for participant with GCPS score of 46 (middle), sagittal slice of cerebellar WM segmentation *in vivo* for participant with GCPS score of 80 (right).



Discussion

The aim of the present study was to determine the associations between self-reported pain intensity and disability, with cerebellar WM volumes in community-dwelling older adults. While self-reported pain intensity was negatively correlated with cerebellar WM volume in older adults, pain disability did not show any significant association with cerebellar WM volume. These results indicate that cerebellar white matter is implicated in pain processing, specifically in the perception of clinical intensity of pain in older individuals.

Support of Existing Literature

These results further support research studies that indicate the cerebellum's key role in somatosensory and pain processing. The two ascending pathways to the cerebellum are well-known: mossy fibers convey the excitatory input from the pontine nuclei to granule cells which bifurcate and synapse on Purkinje cells, a class of GABAergic neurons located in the cerebellum; excitatory cerebellar afferents convey input from the inferior olive to Purkinje cells. In the efferent pathway, cerebellar nuclei project to the brainstem and thalamus, reaching different parts of the cerebral cortex. Direct evidence that the cerebellum receives nociceptive afferents has mainly come from electrophysiological studies which evoked neural activity in the cerebellum with the

stimulation of nociceptors in animal models. In cats, stimulation of cutaneous A-delta and C fiber nociceptors activated climbing fibers that terminate on Purkinje cells in the cerebellar anterior lobe ipsilateral to stimulation (Ekerot et al., 1987). Likewise, in rats, nociceptive visceral stimulation modulated Purkinje cell activity in the posterior cerebellar vermis (Saab and Willis, 2001). The present study further supports that the cerebellum's capacity for nociceptive encoding needs to be explored in both humans and animal models.

Although previous research has demonstrated that whole-brain WM structure changes contribute to the pain–mobility association in older adults, this study focused on potential cerebellar mechanisms. Specific brain areas are likely affected by pain differentially, so by further examining WM structure in a specific region of the brain in this study, changes in total-brain WM measure were assessed more closely. These results support the present hypothesis that similar changes previously observed in the WM of the cerebrum in individuals with musculoskeletal pain, would also be observed in cerebellar WM volume.

The finding that lower WM volume in the cerebellum was associated with higher self-reported chronic pain intensity, but not pain disability, may be explained by the cerebellum's involvement in somatosensory and pain processing that are likely to become dysregulated with age. Previous studies have shown non-uniformity of change in specific cerebellar regions with aging (Andersen et al., 2003), while the cerebellum at the molecular level wholistically ages slowly according to the epigenetic clock (Horvath et al., 2015). Inconsistent activation of the cerebellum with painful stimulus in humans has added to the discrepancy in current literature that also lacks information about the encoding process of nociceptive stimuli in the cerebellum (Helmchen et al., 2003, 2004). While cerebellar WM volume changes have been clearly observed with age, cerebellar WM volume also appears to change with chronic pain in older individuals. Thus, our findings suggest that increased chronic pain may be associated with alterations in cerebellar WM structure, above and beyond the already reported age-related changes.

Limitations

These results are limited by several factors. First only correlations were examined between cerebellar WM and clinical pain in a cross-sectional study, thus causal inferences cannot be made. This is often a limitation of clinical studies as we cannot establish whether chronic pain caused changes to the cerebellar WM, or pre-existing WM structure caused increased pain intensity, or both variables were associated to a third variable. Second, the sample consisted of high functioning, community-dwelling older adults. For this reason, findings cannot be generalized to institutionalized older adults or individuals recruited from pain clinics who often experience more severe levels of pain, along with higher rates of cognitive impairment and co-morbidities. Third, the lack of association in the male sample is likely due to the significantly smaller male sample size and lack of statistical power in this subgroup.

Clinicians have consistently been tasked with relieving human suffering, and the quantitative approach to clinical pain assessment has been developed more recently as a method to capture the cognitive component of pain. Since chronic pain is a multidimensional phenomenon, pain intensity and pain-related disability are important attributes of any chronic pain condition (von Korff et al., 1992). Chronic pain has been extensively measured using self-reported, clinical pain scales, and it is believed that clinical pain disability, in addition to pain intensity, is crucial to monitor and target for treatment purposes. While targeting a decrease in clinical pain intensity is sufficient for short-term alleviation, it does not guarantee the improvement of quality of life. Therefore, while pain intensity remains a determinant in any painful experience, this self-report score has its limitations and other measures such as pain disability and experimental pain should also be considered for the development of targeted therapeutic treatments. For example, quantitative sensory testing (QST) can assess the integrity of the somatosensory system along various levels of the neural axis, from receptor to brain, complementing clinical neurophysiological studies that only measure sensory large fiber function. While this experimental method does not provide information about the exact source of somatosensory dysfunction, it can provide more information about central pathways originating from large myelinated A-beta, thinly myelinated A-delta, and small

unmyelinated C fibers. In addition, QST has been shown to predict treatment response in a number of pain conditions and it may be used to probe different pain mechanisms (Cruz-Almeida and Fillingim, 2014).

Future Directions

Despite these limitations, the findings from this research show the need for further investigation into the impact of chronic pain on the brain during aging. Longitudinal studies can further examine associations between cerebellar WM, pain intensity, and disability, while also examining how these associations may impact physical function performance. Future research is needed to further delineate the role of the cerebellum in older individuals with chronic pain using larger samples including more males.

It is important to recognize that there are regional differences within the cerebellum itself when it comes to aging. Total cerebellar volume remains stable until about 50 years, following which volumes are negatively correlated with age. Regionally, however, the vermis shows clear structural differences across a larger age spectrum, while the lateral hemisphere is not impacted by age at all (Luft et al., 1999). Therefore, examining changes in white matter volume within cerebellar regions previously known to remain constant with age can allow for larger sample sizes to be examined for neurobiological differences related to pain, above and beyond aging.

Additional measures of WM structure such as Mean Diffusivity (MD) and Fractional Anisotropy (FA), will help in answering the next key question about the specific role of white matter in human pain-motor interactions. In the present analysis, Freesurfer's recon-all tool individually masked and labeled each structural MRI image. This has allowed for the development of scripts intended for use with TRACULA, minimizing dependence on image normalization to the Montreal Neurological Institute (MNI) atlas for diffusion tensor image analysis. Since normalization can remove the individual variation of white matter between subjects, utilizing the individual labels created by Freesurfer will now allow for closer examination of the white matter tracts in certain regions of the brain such as the cerebellum. Examining cerebellar white matter

MD and FA values, in addition to WM volume, will further characterize WM integrity, contributing to literature that focuses on white matter in the context of pain, mobility, and aging.

Conclusion

There were significant negative associations between cerebellar WM volume and clinical pain intensity scores. Lower cerebellar white matter volume in participants, particularly older females, was associated with higher clinical pain intensity, but not disability.

An improved understanding of the cerebellar role in the experience of pain has implications for the discovery of new treatments for managing pain. Few studies have discerned cerebellar function as it relates to pain processing, which is a multi-dimensional experience. Based on the evidence available, the cerebellum plays a role in affective pain processing, pain modulation, and sensorimotor processing (Moulton et al., 2010). More research is required to define the role of the cerebellum, particularly its white matter, in human pain processing and its impact on physical function.

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