Psychiatry Research: Neuroimaging 289 (2019) 10–12

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Short Communication

The relationship between hippocampal volume, chronic pain, and depressive symptoms in older adults

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ARTICLE INFO

Keywords:
Depressive symptoms
Chronic pain
Hippocampal volume

ABSTRACT

We aimed to test the hypothesis that the effect of chronic pain on depressive symptoms is mediated through hippocampal volume (HV). Participants were 131 non-demented adults over the age of 70 years from the Einstein Aging Study. Smaller right and left HV were both associated with higher depressive symptoms, but only smaller right HV was associated with chronic pain. In mediation models, right HV was a significant mediator for the effect of chronic pain on depression. Our findings suggest presence of a shared brain substrates between chronic pain and depression as reflected by right HV.

1. Introduction

Depressive symptoms and pain are highly prevalent neuropsychiatric symptoms in older adults. Both conditions often co-occur, share some similar symptoms, and exacerbate one another, suggesting overlapping neurobiological substrate (Goesling et al., 2013; Lin et al., 2003). Both clinical observations and animal studies point to the reciprocal causative relationships between pain and depression. However, the neural mechanisms of this interaction are largely unknown and mechanism-based preclinical studies are rare. Identifying mechanisms that contribute to the development of clinical or subclinical depression and chronic pain in older adults, can open new possibilities for prevention and treatment of these symptoms.

Although the general reciprocal interaction between chronic pain and depression is well documented (Kroenke et al., 2011), the underlying neurobiological mechanisms are unclear. Depression is a persistent and highly heterogeneous disease and human neuroimaging studies reveal structural changes in multiple brain regions, including brain regions that involve pain perception and processing (Tadayonnejad and Ajilore, 2014). Chronic pain also fundamentally alters the brain structure and function as suggested by neuroimaging studies (Baliki et al., 2011). One of the brain regions that is strongly linked with depression and chronic pain is hippocampus. The hippocampus plays an important role in a variety of physiological process, including memory and cognition, mood, stress and pain perception (Eichenbaum, 2004; Ezzati et al., 2014; Videbech and Ravnkilde, 2004b; Zimmerman et al., 2016). A laterality effect has been reported in association of hippocampal volume and function with memory (Shi et al., 2009; Zammit et al., 2017), depression (Videbech and Ravnkilde, 2004b), and pain (Ezzati et al., 2014). These reports indicate a specialized role for left and right hippocampus, with left hippocampus being more essential to verbal and declarative memory and right hippocampus playing a stronger role in depression, pain, and stress.

In the current study, in a sample of older adults from Einstein Aging Study (EAS) we investigated the association of chronic pain and depressive symptoms with HV. We explored if there is laterality effect in this association (i.e. which of left or right HV show stronger association with chronic pain or depressive symptoms. We hypothesized that hippocampal volume loss is more pronounced on the right side in older adults with higher depressive symptoms and chronic pain. Furthermore, we investigated if the potential role of HV as a mediator of the effect of chronic pain on depressive symptoms.

2. Methods

2.1. Study design and participants

The participants were 131 non-demented adults over the age of 70

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https://doi.org/10.1016/j.pscychresns.2019.05.003
Received 30 January 2019; Received in revised form 12 May 2019; Accepted 14 May 2019
Available online 15 May 2019
0925-4927/

years drawn from the Einstein Aging Study (EAS). The study design, sampling, eligibility and exclusion criteria, and other methods of the EAS have been described in detail previously (Katz et al., 2012). Subjects who did not meet standard MRI eligibility criteria were also excluded from this study. All studies were approved by institutional review board (IRB) of Albert Einstein College of Medicine.

2.2. Measurements of depressive symptoms and chronic pain

Depressive symptoms over a one week period were assessed using the 15-item Geriatric Depression Scale (GDS) (Burke et al., 1991). Total GDS scores ranged from 0 to 15, with clinically significant depression defined as GDS of ≥5.

Chronic pain was measured as a ubiquitous exposure in eight body areas (For details please see (McCarthy et al., 2009)). Chronic pain was defined by the presence of pain, in at least 1 location, that was moderate or severe (minimum rating of 4 out of 10) in the previous 3 months, some, most, or all of the time (McCarthy et al., 2009).

2.3. MRI acquisition and processing

Imaging was performed using a 3.0 T MRI scanner (Achieva Quasar TX; Philips Medical Systems, Best, the Netherlands) with a 32-channel head coil (Sense Head Coil; Philips Medical Systems). Details of the imaging protocol has been described previously (Ezzati et al., 2014). T1-weighted volumetric images were processed using the FreeSurfer software package (version 5.3, available at FreeSurfer Developer website). For each subject the estimated total intracranial volume (TICV) and the whole hippocampal formation on each side was estimated using Free Surfer's standard segmentation procedure using a probabilistic brain atlas (Fischl et al., 2002). Details of MRI analysis has been described previously (Ezzati et al., 2014).

2.4. Statistical analyses

We examined the bivariate associations of right and left HVs, depressive symptoms, and chronic pain with demographic variables such as age, education, sex and TICV using the Pearson product-moment correlation coefficient (r) for continuous variables, and independent *t*-test for categorical variables. Multivariate linear regression models were performed to examine the association between chronic pain and depression. Furthermore, linear regression models were used to assess the independent and joint effect of depressive symptoms and chronic pain on left and right HV, while controlling for age, sex, education, and total intracranial volume (TICV) as covariates. To evaluate whether alteration of HV mediates the effects of chronic pain on depressive symptoms, path analyses with maximum likelihood estimation were performed after controlling for age, sex, education, and TICV. Statistical analyses were conducted using SPSS and SPSS-AMOS software (Chicago, IL: SPSS Inc).

3. Results

Participants had a mean age of 78.9 years (SD = 5.18), were 58.8% women, 54.2% white, with an average education of 14.4 years (SD = 3.4). Participants with chronic pain represented 55% of the sample. Overall participants with chronic pain had significantly lower education, but did not differ in age, gender, race, or global cognition (as measured by Blessed Information-Memory-Concentration test). GDS were significantly higher in participants with chronic pain (Supplementary Table 1).

Multivariate regression models showed that chronic pain is associated with higher depressive symptoms ($\beta = 0.25$, $p = 0.005$) after controlling for demographic covariates. Multivariate regression models with left and right HV as outcome and depressive symptoms and chronic pain as predictors are summarized in table 1. Higher depressive symptoms were associated with both smaller left HV, and right HV. However chronic pain was only associated with smaller RHV. In models including both depressive symptoms and chronic pain as predictors and hippocampal volumes as the outcome, the association between GDS with LHV and RHV remained significant, while the association between chronic pain and RHV was attenuated and became insignificant.

Subsequently, we performed a path analysis looking at the direct and indirect (through HV alteration) effect of chronic pain on depressive symptoms (Fig. 1). Considering that chronic pain was only associated with right HV, the constructed path analysis only included the right HV. The path analysis results showed a good fit ($X^2 = 17.7$, degree of freedom = 3, comparative fit index = 0.99, and root mean square error of approximation = 0.19). Models revealed a significant direct effect of chronic pain on depressive symptoms ($\beta = 0.18$, $p = 0.037$), and a significant indirect effect of chronic pain on depressive symptoms mediated by HV ($\beta = 0.04$, $p = 0.029$).

4. Discussion

In this cross-sectional study, we found a strong association between smaller bilateral HV and higher depressive symptoms. Smaller right HV was also associated with chronic pain. In addition, we showed that the effect of chronic pain on depressive symptoms is at least partially mediated by alteration in right HV.

These results are in general in accordance with other neuroimaging studies in older adults (Videbech and Ravnkilde, 2004a) and confirming our previous findings in a unique subsample of the EAS population (Ezzati et al., 2013, 2014). Our results not only show the importance of hippocampal formation in perception of pain and depressive symptoms, but also it might indicate a specialized role for the right hippocampus in mediating the effect of chronic pain on depression. Animal studies have suggested that chronic pain can alter hippocampal morphology and gene expression via chronic stress-induced HPA dysfunction (Blackburn-Munro and Blackburn-Munro, 2001) or through neuromediators like neurokinin-1 and brain-derived neurotrophic factor (BDNF), which are associated with the disease process in depression (Duric and McCarson, 2006). Although a causal relationship cannot be concluded from our cross-sectional results, together with prior research, our results suggest that chronic pain might enhance vulnerability to depression through its adverse effects on HV.

It is noteworthy that in our path analysis, the direct effect of chronic pain on depressive symptoms was stronger than its indirect effect through left HV ($\beta = 0.19$ vs $\beta = 0.04$, respectively). This is most likely because a complex neural network is involved in the process of pain and depression and hippocampus is only one part of this large network (Baliki et al., 2011; Tadayonnejad and Ajilore, 2014).

While our findings are promising, a few limitations should be noted. Considering the cross-sectional nature of study, we could not confirm the causal relationships. The reduction in HV might predispose individuals to increased pain and increased depressive symptoms. Alternatively, chronic pain and depression may result in hippocampal atrophy. We evaluated pain during the 3-month period before acquiring images, but not before that, and therefore we cannot assess cumulative effects of pain. Finally, the effect of pain medications on outcomes was not assessed in this study.

In conclusion, our study indicates the important interplay between hippocampal volume, depressive symptoms and chronic pain. Presence of chronic pain is potentially a risk factor for occurrence of depression in subjects with smaller RHV.

Acknowledgments

Funding: This research was supported in part by National Institutes of Health grants NIA 2 P01 AG03949, NIA 1R01AG039409-01, NIA R03 AG045474, NIH K01AG054700, the Leonard and Sylvia Marx Foundation, and the Czap Foundation.

Table 1
Regression models predicting left and right hippocampal volume.

Outcome	Predictor	Model 1			Model 2			Model 3		
		B	t	p	β	t	p	β	t	p
LHV	GDS	−0.26	−3.30	0.001				−0.25	−3.05	0.003
	Chronic pain				−0.10	−1.26	0.210	−0.04	−0.50	0.601
RHV	GDS	−0.26	−3.52	0.001				−0.22	−2.96	0.004
	Chronic pain				−0.20	−2.67	0.009	−0.14	−1.92	0.057

GDS: Geriatric depression scale, TICV: Total intracranial volume. LHV = Left hippocampal volume. RHV = Right hippocampal volume.
All models include age, gender, education level, and total intracranial volume as covariates.

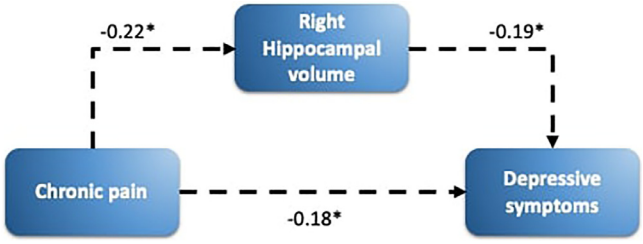

Fig. 1. Schematic diagram of the path analyses for depressive symptoms. Total Hippocampal volume, which correlated with both chronic pain and depressive symptoms was entered as mediator variables for depressive symptoms. Chronic pain was entered as predictor. Age, sex, intracranial volume, and clinical diagnosis were entered as covariates. Significant paths are marked with * sign.

Conflict of Interest Disclosures

None reported.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2019.05.003.

References

Baliki, M.N., Schnitzer, T.J., Bauer, W.R., Apkarian, A.V., 2011. Brain morphological signatures for chronic pain. PloS One 6, e26010.
Blackburn-Munro, G., Blackburn-Munro, R., 2001. Chronic pain, chronic stress and depression: coincidence or consequence? J. Neuroendocrinol. 13, 1009–1023.
Burke, W.J., Roccaforte, W.H., Wengel, S.P., 1991. The short form of the Geriatric Depression Scale: a comparison with the 30-item form. Top. Geriatrics 4, 173–178.
Duric, V., McCarson, K.E., 2006. Persistent pain produces stress-like alterations in hippocampal neurogenesis and gene expression. J. Pain 7, 544–555.
Eichenbaum, H., 2004. Hippocampus: cognitive processes and neural representations that underlie declarative memory. Neuron 44, 109–120.
Ezzati, A., Zimmerman, M.E., Katz, M.J., Lipton, R.B., 2013. Hippocampal correlates of depression in healthy elderly adults. Hippocampus 23, 1137–1142.
Ezzati, A., Zimmerman, M.E., Katz, M.J., Sundermann, E.E., Smith, J.L., Lipton, M.L., Lipton, R.B., 2014. Hippocampal subfields differentially correlate with chronic pain in older adults. Brain Res. 1573, 54–62.
Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., Dale, A.M., 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33, 341–355.
Goesling, J., Clauw, D.J., Hassett, A.L., 2013. Pain and depression: an integrative review of neurobiological and psychological factors. Curr. Psychiatry Rep. 15, 1–8.
Katz, M.J., Lipton, R.B., Hall, C.B., Zimmerman, M.E., Sanders, A.E., Verghese, J., Dickson, D.W., Derby, C.A., 2012. Age-specific and sex-specific prevalence and incidence of mild cognitive impairment, dementia, and Alzheimer dementia in blacks and whites: a report from the Einstein Aging Study. Alzheimer Dis. Assoc. Disord. 26, 335–343.
Kroenke, K., Wu, J., Bair, M.J., Krebs, E.E., Damush, T.M., Tu, W., 2011. Reciprocal relationship between pain and depression: a 12-month longitudinal analysis in primary care. J. Pain 12, 964–973.
Lin, E.H., Katon, W., Von Korff, M., Tang, L., Williams Jr., J.W., Kroenke, K., Hunkeler, E., Harpole, L., Hegel, M., Arean, P., Hoffing, M., Della Penna, R., Langston, C., Unutzer, J., 2003. Effect of improving depression care on pain and functional outcomes among older adults with arthritis: a randomized controlled trial. Jama 290, 2428–2429.
McCarthy, L.H., Bigal, M.E., Katz, M., Derby, C., Lipton, R.B., 2009. Chronic pain and obesity in elderly people: results from the Einstein aging study. J. Am. Geriatrics Soc. 57, 115–119.
Shi, F., Liu, B., Zhou, Y., Yu, C., Jiang, T., 2009. Hippocampal volume and asymmetry in mild cognitive impairment and Alzheimer's disease: Meta-analyses of MRI studies. Hippocampus 19, 1055–1064.
Tadayonnejad, R., Ajilore, O., 2014. Brain network dysfunction in late-life depression: a literature review. J. Geriatric Psychiatry Neurol. 27, 5–12.
Videbech, P., Ravnkilde, B., 2004a. Hippocampal volume and depression: a meta-analysis of MRI studies. The Am. J. Psychiatry 161, 1957–1966.
Videbech, P., Ravnkilde, B., 2004b. Hippocampal volume and depression: a meta-analysis of MRI studies. Am. J. Psychiatry 161, 1957–1966.
Zammit, A.R., Ezzati, A., Katz, M.J., Zimmerman, M.E., Lipton, M.L., Sliwinski, M.J., Lipton, R.B., 2017. The association of visual memory with hippocampal volume. PloS One 12, e0187851.
Zimmerman, M.E., Ezzati, A., Katz, M.J., Lipton, M.L., Brickman, A.M., Sliwinski, M.J., Lipton, R.B., 2016. Perceived stress is differentially related to hippocampal subfield volumes among older adults. PloS One 11, e0154530.