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Research Report

Hippocampal subfields differentially correlate with chronic pain in older adults

Ali Ezzati[a,b,*], Molly E. Zimmerman[a], Mindy J. Katz[a], Erin E. Sundermann[a], Jeremy L. Smith[c,d], Michael L. Lipton[c,d,e,f,g], Richard B. Lipton[a,h]

[a]Saul B. Korey Department of Neurology, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY 10461, USA
[b]Department of Medicine, Montefiore Medical Center, 111 East 210th Street, Bronx, NY 10467, USA
[c]The Gruss Magnetic Resonance Research Center, Albert Einstein College of Medicine of Yeshiva University, Bronx, NY 10461, USA
[d]Department of Radiology, Albert Einstein College of Medicine of Yeshiva University, 1300 Morris Park Avenue, Bronx, NY 10461, USA
[e]The Department of Radiology, Montefiore Medical Center, 111 East 210th Street, Bronx, NY 10467, USA
[f]Department of Psychiatry & Behavioral Sciences, Albert Einstein College of Medicine of Yeshiva University, 1300 Morris Park Avenue, Bronx, NY 10461, USA
[g]The Dominick P Purpura Department of Neuroscience, Albert Einstein College of Medicine of Yeshiva University, 1300 Morris Park Avenue, Bronx, NY 10461, USA
[h]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY 10461, USA

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ABSTRACT

Although previous studies have demonstrated that the hippocampus plays a role in pain processing, the role of hippocampal subfields is uncertain. The goal of this study was to examine the relationship between hippocampal subfield volumes and chronic pain in nondemented older adults. The study sample included 86 community-residing adults age 70 or older who were free of dementia and recruited from the Einstein Aging Study. Chronic pain was defined as pain over the last 3 months, that was moderate or severe (minimum rating of 4 out of 10) most, or all of the time. Hippocampal subfield volumes were estimated using FreeSurfer software. We modeled the association between chronic pain and hippocampal and subfield volume using linear regression. The sample had a mean age of 80 and was 58% female. Chronic pain, present in 55% of the sample, was associated with smaller right and total hippocampal volumes, particularly in women, after adjusting for age, education, and intracranial volume (eTICV). In addition, in women, volume was significantly reduced in participants with chronic pain in right CA2–3 ($\beta = -0.35$, $p = 0.010$), right CA4-DG ($\beta = -0.35$, $p = 0.011$), left presubiculum ($\beta = -0.29$, $p = 0.030$), and left fimbria ($\beta = -0.30$, $p = 0.023$). In men,

*Corresponding author at: Department of Neurology, Albert Einstein College of Medicine, 1165 Morris Park Avenue, Rousso Building, Room 330, Bronx, NY 10461, USA. Fax: +1 718 430 3857.
E-mail address: ali.ezzati@einstein.yu.edu (A. Ezzati).

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chronic pain was not associated with the volume of any of the hippocampal subfield volumes. Chronic pain in women is associated with a reduction in the volume of right hippocampus and also selected hippocampal subfields. Future studies should clarify the mechanisms underlying the association between regional hippocampal volumes and chronic pain, particularly in women.

1. Inroduction

Chronic pain occurs in more than half of older adults resulting in reductions in daily activities and decrements in health-related quality of life. The prevalence of disabling pain increases sharply amongst elderly individuals, especially the oldest-old (Thomas et al., 2004, 2007). It is therefore important to understand both the factors that contribute to the development or acceleration of pain in the elderly as well as its consequences.

Reasons for the increasing prevalence of pain in older adults are not fully understood. Painful conditions such as osteoarthritis are more common in the elderly, which leads to increased peripheral nociception (Oliveria et al., 1995). In addition, aging is associated with widespread changes in the cellular and neurochemical substrates of the nervous system, including the nociceptive system. The functional consequences of biological age-related changes are difficult to extrapolate given the highly-integrated nature of pain processing, but it is clear that there is a relationship between changes in neurobiological structure and function and the experience of pain (Gibson and Farrell, 2004).

Overall pain prevalence is higher in females than males across the entire life span, though certain pain disorders have a male predilection (Fillingim et al., 2009). It has been suggested that different biological mechanisms such as gonadal hormones and endogenous pain modulatory systems, as well as psychological mechanisms including cognitive or affective factors may contribute to sex differences in pain and analgesic responses (Fillingim et al., 2009). However, it is still unclear which biological mechanisms contribute to this gender difference in pain perception.

The hippocampus plays an important role in a variety of physiological processes including memory, mood and stress (Price and Drevets, 2010; Zimmerman et al., 2008). Many investigators have evaluated the role of the hippocampus in pain processing in human and animal studies (Bingel et al., 2002; Duric and McCarson, 2006; Schweinhardt et al., 2006; Zimmerman et al., 2009). Neuroimaging studies have shown that the hippocampus is activated in response to painful stimuli in healthy volunteers (Bingel et al., 2002). Furthermore, adults with chronic pain syndromes have functional and anatomical alterations in brain regions involved in pain processing including the hippocampus, the thalamus, the basal ganglia and amygdala as well as cingulate, prefrontal and somatosensory cortex (Schweinhardt and Bushnell, 2010). In older adults, higher levels of pain severity have been associated with both reductions in hippocampal volume (HV) and lower NAA levels in the hippocampus (Zimmerman et al., 2009). Alterations in specific transmitters have been demonstrated. For example, patients with fibromyalgia have decreased presynaptic dopaminergic activity was evident in several brain regions, including the hippocampus (Schweinhardt et al., 2006).

The hippocampal formation consists of various subfields (subregions) including CA1–CA4, dentate gyrus (DG), fimbria, presubiculum, and subiculum. These subfields differ in histology, connectivity and function (Fanselow and Dong, 2010).

Table 1 – Sample demographics, TPI scores, and hippocampal measurements.

	Total sample, mean (SD)	NCP group mean (SD)	CP group mean (SD)	*p*-Value[b]
Sample size	86	39	47	
% Women	65.1	53.8	74.4	0.046
% White	54.7	59	51.1	0.515
% Right handed	89.5	92.3	87.2	0.444
Age, years	80.23 (4.82)	80.02 (4.99)	80.40 (4.72)	0.722
Education, years	14.21 (3.57)	15.18 (2.99)	13.40 (3.83)	0.021
TPI	4.34 (6.57)	0.30 (0.48)	7.69 (7.37)	<0.001
FCSRT-IR free recall score	32.06 (6.78)	32.38 (7.25)	31.79 (6.44)	0.690
FCSRT-IR total recall score	47.24 (2.55)	47.54 (1.16)	47.00 (3.29)	0.334
Left hippocampal volume	3.19 (0.40)	3.28 (0.38)	3.13 (0.41)	0.076
Right hippocampal volume	3.27 (0.44)	3.39 (0.34)	3.15 (0.49)	0.010
Total hippocampal volume [a]	6.46 (0.78)	6.67 (0.63)	6.28 (0.84)	0.018
eTICV	1340 (202)	1382 (197)	1305 (201)	0.078

CP=Chronic pain, NCP=No chronic pain, TPI=Total Pain Index; FCSRT-IR=Buschke and Grober Free and Cued Selective Reminding Test-Immediate Recall; and eTICV=estimated Total Intracranial Volume.

[a] MRI volumetric data are given in cubic centimeters.

[b] Using *t*-test for continuous variables, and Chi-square test for categorical variables.