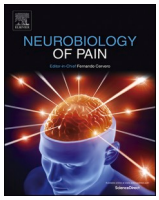
Neurobiology of Pain 14 (2023) 100137

Contents lists available at ScienceDirect

Neurobiology of Pain

journal homepage: www.sciencedirect.com/journal/neurobiology-of-pain



Hippocampal volume changes across developmental periods in female migraineurs

Sophie L. Wilcox [a,1], Sarah Nelson [b,1,*], Allison Ludwick [a], Andrew M. Youssef [c], Alyssa Lebel [a,d], Lino Beccera [a,e], Rami Burstein [f], David Borsook [g]

[a] Center for Pain and the Brain, Harvard Medical School, Boston, MA, USA
[b] Department of Psychiatry, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
[c] Department of Anatomy and Histology, The University of Sydney, Sydney, NSW, Australia
[d] Pediatric Headache Program, Boston Children's Hospital, Waltham, MA, USA
[e] Invicro, Boston, MA, USA
[f] Anesthesia and Critical Care, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
[g] Department of Psychiatry and Department of Radiology, Massachusetts General Hospital, Boston, MA, USA

ARTICLE INFO

Keywords:
Headache
Migraine
Brain
Development
Stress

ABSTRACT

Brain-related plasticity can occur at a significant rate varying on the developmental period. Adolescence in particular has been identified as a period of growth and change across the structure and function of the nervous system. Notably, research has identified migraines as common in both pediatric and adult populations, but evidence suggests that the phenotype for migraines may differ in these cohorts due to the unique needs of each developmental period. Accordingly, primary aims of this study were to define hippocampal structure in females (7–27 years of age) with and without migraine, and to determine whether this differs across developmental stages (i.e., childhood, adolescence, and young adulthood). Hippocampal volume was quantified based on high-resolution structural MRI using FMRIB's Integrated Registration and Segmentation Tool. Results indicated that migraine and age may have an interactional relationship with hippocampal volume, such that, while hippocampal volumes were lower in female migraineurs (compared to age-matched controls) during childhood and adolescence, this contrast differed during young adulthood whereby hippocampal volumes were higher in migraineurs (compared to age-matched controls). Subsequent vertex analysis localized this interaction effect in hippocampal volume to displacement of the anterior hippocampus. The transition of hippocampal volume during adolescent development in migraineurs suggests that hippocampal plasticity may dynamically reflect components of migraine that change over the lifespan, exerting possible altered responsivity to stress related to migraine attacks thus having physiological expression and psychosocial impact.

Introduction

Migraine attacks are more common in post-pubertal girls and have a high incidence in adolescence and peak in early adulthood (King et al., 2011). Within this demographic, migraines can be a significant health concern that interferes with daily functioning including missed school/college (e.g., absences, late arrivals), social isolation or withdrawal, and particularly in the younger age group, an increased risk of developing psychological impairment such as symptoms of anxiety, depression, or catastrophizing, etc. (Simons et al., 2015; Kashikar-Zuck et al., 2013; Krogh et al., 2015). The period of development during the transition from childhood, through adolescence and to early adulthood marks a critical period for neurodevelopment, centering on puberty (Satterthwaite et al., 2014). Headache duration, laterality, and spatial distribution are notable features that may present differently in children and adolescents, when compared to adult populations (Hershey et al., 2005). Furthermore, the prevalence of migraine increases with age during this period, with differences observed across sexes. Specifically, prior to puberty, the incidence of migraine is equally prevalent across males and females, whereas after puberty incidence increases sharply for females while remaining consistent for males (Lipton and Bigal, 2005). Despite these well-known differences in presentation, the mechanisms

* Corresponding author.
E-mail address: sarah.nelson@childrens.harvard.edu (S. Nelson).
[1] Co-first authors.

https://doi.org/10.1016/j.ynpai.2023.100137
Received 2 May 2023; Received in revised form 22 June 2023; Accepted 23 June 2023
Available online 24 June 2023

by which neurodevelopment may influence the prevalence and presentation of migraine across younger developmental periods and conversely, how migraine may interact with brain development are still not fully understood (Maleki et al., 2016).

The potential interaction between migraine and neurological development in childhood and adolescence is of particular importance when migraine is considered in the context of its potential to enact persistent, reoccurring physiological and psychological stress (Borsook et al., 2012; Maleki et al., 2012). Short-term activation of the hypothalamic–pituitary–adrenal (HPA) axis in response to stress such as that which occurs in the context of acute pain (i.e. headache, injury) and the subsequent release of glucocorticoids have adaptive consequences (Chapman et al., 2008). Whereas prolonged elevation of glucocorticoids in response to repeated or prolonged stress, such as that which occurs in conjunction with chronic pain episodes (e.g., repeated migraine attacks), can have deleterious effects (Huss et al., 2009; Leistad et al., 2007). Increasing evidence in pre-clinical models suggests that prolonged or repeated exposure to high levels of glucocorticoids results in significant alterations in hippocampal structure (McEwen, 2001). In adults with a history of migraine, similar alterations in hippocampal structure have been observed, whereby hippocampal volume decreases with an increasing total number of migraine attacks (Maleki et al., 2013). In a large cohort of adults, evidence was also found associating hippocampal volume with the number of body pain sites (Lobo et al., 2022) and increased pain sensitivity (Mutso et al., 2012). The hippocampus has also been strongly implicated as playing a role in the fear network, which is strongly and intricately related to pain processing (Ziv et al., 2010; Duric and McCarson, 2006; Liu and Chen, 2009). In peripubertal animal paradigms, chronic stress produces alterations in hippocampal volume, and stress (HPA) axis functioning (Isgor et al., 2004). Similarly, in youth populations outside of pain, research also has shown that prolonged stress exposure such as adverse childhood experiences (e.g., abuse/neglect) can deleteriously impact hippocampal structure and function (Carrion et al., 2007). However, the potential similarities or differences in hippocampal structure across child/adolescent and adult individuals with migraines is still unclear.

Preliminary investigation demonstrated development-specific differences in brain structure and function, including the hippocampus, in pediatric migraine (Faria et al., 2015), but the trajectory of these changes over the lifespan from child to adult has not yet been considered. Accordingly, the primary aim of this study was to define hippocampal structure in female patients with migraines starting from childhood into early adulthood (ages 7 to 27 years) in comparison to matched healthy controls. Specifically, we compared hippocampal structure at distinct developmental stages (childhood, adolescence, and early adulthood). As we also sought to assess the association between individual migraine characteristics (duration and frequency) with hippocampal volume at each developmental time period. We hypothesized that differences in hippocampal volume would be observed in the three groups separate from the normal development trajectory observed in these age groups vs. healthy controls.

Materials and methods

Participants

Participants from 3 migraine-imaging studies were included and pooled into one large cohort in a case-controlled, cross-sectional investigation. *A priori* calculations were performed to confirm appropriate sample sizes. Participants were not included if they possessed any other headache diagnosis (e.g., tension-type headache, new daily persistent headache). Both migraine and matched control participants were scanned at the same location and using the same parameters. Only female participants were included to avoid a confound of sex. All migraine participants met diagnostic criteria for migraine as defined by the International Classification of Headache Disorders, second edition (ICHD-2) (The International Classification of Headache Disorders, 2004). Prior to consent, a study physician confirmed all patient diagnoses during a clinical interview. Individuals were excluded if they had continuous background headache (or pain) and/or were taking prophylactic migraine treatment. Age-, sex- and pubertal-matched controls were recruited through advertisements in the greater Boston area. Across both groups (migraine and healthy control), individuals were excluded if they had significant medical problems such as uncontrollable asthma and seizures, cardiac diseases, severe psychiatric disorders, and neurological disorders other than migraine. For MRI safety reasons participants were excluded if they were pregnant, claustrophobic, and/or had metallic implants or devices.

Informed written consent was obtained from all individuals prior to participation. When participants were under the age of 18, consent was also obtained from a parent or guardian. Each study received formal Institutional Review Board approval (Boston Children's Hospital and McLean Hospital, USA) and were conducted in accordance with the Declaration of Helsinki and the International Association for the Study of Pain criteria for performing human pain investigations. Structural analysis from one of these studies has previously been reported (Faria et al., 2015).

Questionnaires

Demographic, general medical and headache specific questionnaires were administered, as relevant, to all participants. A general medical questionnaire was also administered and included questions regarding menstrual status. A headache history questionnaire included questions regarding age of migraine onset, episode frequency (migraines per month), episode duration (in hours), pain intensity and unpleasantness (0–10 numericratingscale), accompanying symptoms (including nausea, vomiting, photophobia and phonophobia), and medication usage.

MRI acquisition

All participants underwent imaging on a Trio 3T whole body scanner (Siemens Medical Solutions USA Inc., Malvern, PA). Specific details relating to MRI acquisition have been previously reported in another investigation using these data. See Colon, et al., 2019 (Colon et al., 2019) for further information. For image registration, a high-resolution T1-weighted anatomical image was collected using a magnetization-prepared, rapid-acquisition gradient-echo (MPRAGE) (176 slice; slice thickness = 1 mm; TR = 2520 ms; TE = 1.74 ms; TI = 800 ms; FOV = 220 mm2, matrix size = 220 × 220).

MRI quality assurance

Quality assurance of the MRI data was performed retrospectively using standardized image quality rating scale (https://research.cchmc.org/c-mind/8-quality-assurance-procedures). T1-weighted anatomical image were visually inspected and excluded for serious or excessive image artifacts, intensity variation across the FOV and/or poor tissue contrast. All final images passed quality assessment. To account for potential image quality differences between studies (due to different scanners, sequences and protocols) a retrospective QA framework for empirical quantification of image quality was also implemented. All anatomical images were preprocessed using the quality assurance module of the Computation Anatomical Toolbox (CAT12) (http://dbm.neuro.uni-jena.de/cat/) within SPM12 and Matlab (R2015a, Mathworks Inc.). Image parameters including noise, inhomogeneities (bias) and resolution are summarized to a single quality rating and scaled to a common rating scale for comparison. The weighted average quality score ranged from 83 to 87 (on a 1–100 scale). Scores within the range of 80–90 are classified as "good" quality). Furthermore, the mean quality score did not significantly differ between the three studies ($F(2,117) = 0.332$, $p = 0.718$), as shown in Supplemental Fig. 1.

MRI analyses

Volumetric quantification: Total brain and hippocampal volumes were estimated using FMRIB's Integrated Registration and Segmentation Tool (FIRST) (Patenaude et al., 2011) for subcortical structures, part of the FMRIB's Software Library (FSL v5.0.6). FIRST was run as part of FSL's general pipeline for processing anatomical T1-weighted images (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/fsl_anat). In brief, prior stages in the pipeline include reorientation, field of view cropping, bias field correction, registration to standard space, brain extraction, and tissue-type segmentation.

For volumetric analysis FIRST comprises of three processing stages including registration, segmentation and boundary correction. Images are registered using a standard 12 degrees of freedom affine registration to the non-linear MNI152 template at 1 mm resolution. This registration is subsequently repeated using sub-cortical mask to optimize alignment. For segmentation FIRST uses a Bayesian probabilistic model that relies on shape and intensity to infer the fitting of subcortical structures. For each structure a pre-defined number of modes of variation is applied to ensure the best fit. The models incorporated in FIRST are deformable meshes of 15 subcortical structures (including the left and right hippocampus) constructed from manually segmented images. This manually segmented training data included 336 subjects, consisting of both children and adults, and controls and patients. The mesh-based representations of a segmented structure are then converted to volumetric representations using intensity-based boundary correction (Patenaude et al., 2011). Registration, segmentation and boundary correction were individually reviewed and visually verified for all subjects based on the Harmonized Hippocampal Protocol (Boccardi et al., 2015; Frisoni et al., 2015). Fig. 1 demonstrates the segmentation of the hippocampus.

A voxel count was then used to estimate volumes of the left and right hippocampus separately in mm^3. Normalized hippocampal volumes were obtained by multiplying the estimated volumes by a volumetric scaling factor to normalize for total brain volume.

Statistical analyses

Statistical analyses of hippocampal volumes were performed with IBM SPSS Statistics (version 23). To begin, a factorial, between-subjects analysis of variance (ANOVA) was conducted to assess the main effects of condition (2 levels: migraine, control) and developmental stage (3 levels: children, adolescents, and young adults), and the interaction effect between them (i.e., condition × development). Hippocampal volumes were assessed separately for the left and right hemisphere. They were entered into the model as independent variables, with condition and development included as fixed factors. In the case of a significant interaction effect, post-hoc pairwise comparisons of condition (i.e., migraine versus control) at each developmental stage were conducted. An alpha level of 0.05 was considered significant for all statistical tests. Assumptions of normality and homogeneity of variances were not violated. To test for a significant confound of imaging study, an exploratory analysis in healthy controls compared hippocampal volumes between imaging studies, within each developmental stage. No significant differences between studies were observed (see Supplemental Fig. 2).

Within migraine participants, a series of linear regressions were conducted to examine the association between headache characteristics (i.e., disease duration and headache frequency) and hippocampal volumes. Disease duration was examined as a partial correlation, controlling for age, as age and disease duration were significantly correlated overall, but not within individual development stages (all migraine subjects $r = 0.523$, $p < 0.001$; children – $r = 0.332$, $p = 0.152$; adolescents – $r = 0.091$, $p = 0.702$; young adults – $r = -0.125$, $p = 0.598$). Hippocampal volumes were assessed separately for the left and right. An alpha level of 0.05 was considered significant for all correlations.

Vertex analysis

Vertex analysis was performed using FSL's FIRST, as described above, to localize hippocampal shape differences. For each participant's mesh-based representation of the hippocampus, the vertex locations are projected onto the surface of the cohort's average shape transformed to Montreal Neurological Institute space. These projection values represent the perpendicular distance from the average surface. Statistical analyses of these scalar projection values were conducted using univariate permutation methods using FSL's *randomise* tool, using cluster-based (cluster size) thresholding corrected for multiple comparisons at an alpha level of 0.05 (cluster forming threshold [F value]$m > 4.1$, cluster extent > 30 contiguous vertices). Between-group comparisons for condition (i.e., migraine versus controls), at each developmental stage, were performed for both the left and right hippocampus with 5000 permutations. In order to determine whether these clusters represent greater inward/outward displacement (i.e., growth or atrophy) from the average hippocampal shape, as indicated by their negative/positive vales respectively, the mean scalar projection values were extracted for each subject using the *fslstats* command line utility for summary statistics.

Results

Participant demographics

The final participant sample consisted of 120 females (60 patients with migraine and 60 healthy controls) with a mean (±SD) age of 16.1 ± 5.3 years (range 7 to 27 years of age). No incidental findings were present for these selected participants. Migraine and control matches were grouped according to developmental stages, with children defined as prepubertal (pre-menarche) and between 7 and 12 years ($n = 40$), adolescents defined as pubertal (post-menarche) and between 12 and 18 years ($n = 40$) and young adults defined as between 18 and 27 years ($n = 40$). Table 1 provides an overview of sample demographic characteristics.

Migraine-related clinical variables

A summary of migraine-related clinical variables, overall and by

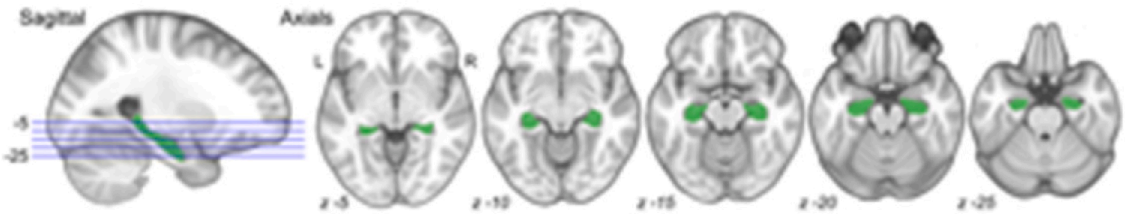


Fig. 1. Hippocampal segmentation. An example of FIRST's segmentation of the hippocampus is shown in green, overlaying the T1-weighted anatomical image. The hippocampus is shown in sequential axial slices from rostral to caudal. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Demographic characteristics of the study participants.

	Overall		Childhood		Adolescence		Young adult	
	Control	Migraine	Control	Migraine	Control	Migraine	Control	Migraine
N	60	60	20	20	20	20	20	20
Age (mean ± SD range)	16.1 ± 5.4 8.2–27.9	16.3 ± 5.5 7.3–26.3	10.0 ± 1.1 8.2–11.8	10.2 ± 1.6 7.3–12.5	15.8 ± 1.7 11.9–18.6	15.7 ± 1.5 12.0–17.7	22.4 ± 2.6 18.2–27.9	22.9 ± 2.1 19.3–26.3

developmental stage, is presented in Table 2. The mean age at migraine onset significantly differed between the developmental stages, with young adult migraineurs having a later average age of onset compared to both child and adolescent migraineurs (Age of onset [mean ± SD]: children 6.9 ± 2.2, adolescents 8.9 ± 3.9 and young adults 14.8 ± 3.7, $F(2,57) = 29.3$, $p < 0.001$). The mean disease duration also significantly differed between the developmental stages, with adolescents and young adults having a longer duration than children (Disease duration [mean ± SD]: children 3.1 ± 2.1, adolescents 6.6 ± 3.7and young adults 8.2 ± 3.8, $F(2,57) = 13.1$, $p < 0.001$). In contrast, the mean frequency of migraine attacks per month (mean ± SD: overall 4.1 ± 3.7), the duration of migraine attacks (mean ± SD: overall 11.1 ± 13.1 h), pain intensity (mean ± SD: overall 8.2 ± 1.5) and pain unpleasantness (mean ± SD: overall 8.3 ± 1.5) did not significantly differ between developmental stages.

Hippocampal volume

For both the left and right hippocampal volumes, an analysis of variance yielded a significant main effect of condition (left - $F(1,114) = 4.996$, $p = 0.027$; right - $F(1,114) = 3.963$, $p = 0.049$), such that on average hippocampal volume was lower for migraineurs (mean ± SE: left – 3428.3 ± 176.6; right – 3539.6 ± 182.6) compared to healthy controls (mean ± SE: left – 3922.0 ± 169.8, right – 3980.8 ± 170.7). The main effect of development stage was also significant (left - $F(2,114) = 9.269$, $p < 0.001$; right - $F(2,114) = 10.453$, $p < 0.001$), such that on average hippocampal volume were significantly higher in young adults (mean ± SE: left – 4345.9 ± 191.0, right – 4471.4 ± 199.1) compared to both children (mean ± SE: left – 3298.5 ± 192.0, right – 3329.3 ± 175.4) and adolescents (mean ± SE: left – 3381.1 ± 223.9, right – 3480.0 ± 235.3) (young adults vs. adolescents: left – $p = 0.001$, right – $p < 0.001$; young adults vs. children: left – $p < 0.001$, right – $p < 0.001$; adolescents vs. children: left – $p = 0.761$, right – $p = 0.580$).

However, the interaction effect was also significant (left - $F(2,114) = 6.302$, $p = 0.003$; right - $F(2,114) = 7.617$, $p = 0.001$), indicating that the effect of condition on hippocampal volumes varied across the development stages. As shown in Fig. 2, post-hoc comparisons indicated that in children hippocampal volumes were significantly lower in migraineurs in comparison to healthy controls (mean difference: left = −981.2, p = 0.012; right = −890.0, $p = 0.022$). Similarly, in adolescents, hippocampal volumes were significantly lower in migraineurs in comparison to healthy controls (mean difference: left = −1112.4, $p = 0.004$; right = −1202.3, $p = 0.002$). Conversely, in young adults, hippocampal volumes were significantly higher in migraineurs, but only for the right hippocampus, in comparison to healthy controls (mean difference: left = 612.7, $p = 0.112$; right = 768.8, $p = 0.048$).

Hippocampal volume and clinical metrics

For both the left and right hippocampus, headache frequency was not significantly correlated with volume for migraineurs overall (left – r = 0.214, $p = 0.107$, 95% CI [−17.2, 172.3]; right – r = 0.188, $p = 0.159$, 95% CI [−28.3, 168.9]), or for migraineurs within each developmental stage (children: left – r = −0.371, $p = 0.118$, 95% CI [−143.9, 17.8]; right – r = −0.354, $p = 0.136$, 95% CI [−128.0, 19.1]. Adolescents: left – r = 0.076, $p = 0.756$, 95% CI [−235.4, 318.4]; right – r = 0.167, $p = 0.495$, 95% CI [−184.6, 366.8]. Young adults: left – r = 0.254, $p = 0.280$, 95% CI [−59.2, 193.1]; right – r = 0.079, $p = 0.742$, 95% CI [−112.9, 155.6]). Furthermore, for both the left and right hippocampus, disease duration was not significantly correlated with volume for migraineurs overall (left – r = −0.200, $p = 0.128$, 95% CI [−166.1, 21.5]; right – r = −0.217, $p = 0.098$, 95% CI [−177.6, 15.5]), or for migraineurs within each developmental stage (children: left – r = 0.054, $p = 0.826$, 95% CI [−154.0, 190.6]; right – r = 0.130, $p = 0.595$, 95% CI [−114.5, 193.6]. Adolescents: left – r = −0.270, $p = 0.263$, 95% CI [−268.9, 78.3]; right – r = −0.314, $p = 0.191$, 95% CI [−284.3, 61.2].

Table 2
Migraine-related clinical variables, overall and by development group.

	Overall	Childhood	Adolescence	Young adult	Test statistic	df	P
	N = 60	N = 20	N = 20	N = 20			
Migraine with aura (% Within group)	33.3%	26.3%	38.9%	35.0%	$\chi^2 = 0.7$	2	0.706
Age of onset (Mean ± SD)	10.2 ± 4.7	6.9 ± 2.2	8.9 ± 3.9	14.8 ± 3.7	F = 29.3	2,57	0.000*
Disease duration (Mean ± SD)	6.0 ± 3.9	3.1 ± 2.1	6.6 ± 3.7	8.2 ± 3.8	F = 13.1	2,57	0.000#
Migraine frequency (per month) (Mean ± SD)	4.1 ± 3.7	3.4 ± 3.9	3.4 ± 2.3	5.5 ± 44	F = 2.2	2,55	0.119
Migraine duration (hours) (Mean ± SD)	11.1 ± 13.1	10. ± 18.5	12.4 ± 10.2	11.3 ± 9.9	F = 0.1	2,51	0.871
Pain intensity (0–10 NRS) (Mean ± SD)	8.2 ± 1.5	7.8 ± 2.1	8.2 ± 1.2	8.5 ± 1.1	F = 1.1	2,56	0.338
Pain unpleasantness (0–10 NRS) (Mean ± SD)	8.3 ± 1.5	8.0 ± 2.0	8.5 ± 1.3	8.6 ± 1.1	F = 0.9	2,56	0.426

* Post-hoc comparisons: Childhood vs. Adolescence, mean difference = −1.98, p = 0.068; Childhood vs. Young adult, mean difference = −7.83, p < 0.001; Adolescence vs. Young adult, mean difference = −5.85, p < 0.001

Post-hoc comparisons: Childhood vs. Adolescence, mean difference = −3.45, p = 0.001; Childhood vs. Young adult, mean difference = −5.05, p < 0.001; Adolescence vs. Young adult, mean difference = −1.60, p = 0.118

NRS – numeric rating scale

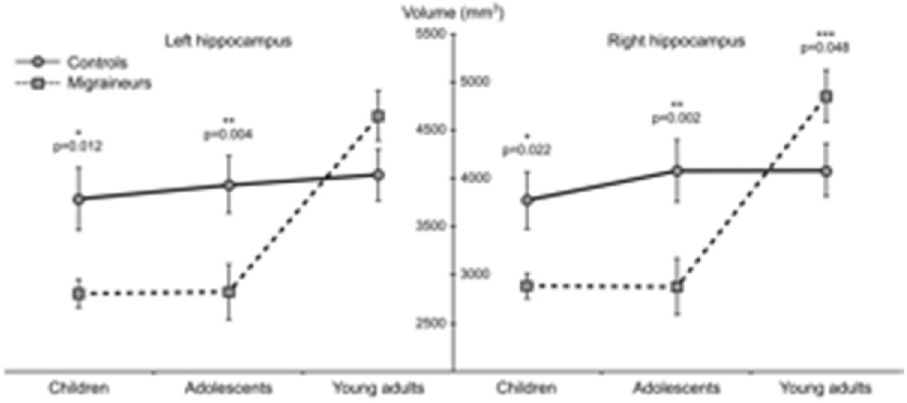


Fig. 2. Line graphs of mean hippocampal volume, for both the left and right hippocampi, comparing migraineurs to healthy controls at each development stage (children, adolescents and young adults). Error bars represent the standard error of the mean. Statistically significant differences are indicated with asterisks ($p < 0.05$).

Young adults: left – r = −0.205, $p = 0.400$, 95% CI [−231.4, 96.9]; right – r = −0.295, $p = 0.221$, 95% CI [−258.9, 64.1]).

Hippocampal shape

Hippocampal shape results using vertex analysis revealed significant alterations from the standard structure of the hippocampus in the migraine group vs healthy controls, as shown in Fig. 3. In children, the migraine group showed a significant inward displacement in the dorsal posterior hippocampus bilaterally and the ventral anterior hippocampus unilaterally (left). In adolescents, the migraine group showed a significant inward displacement in the dorsal anterior hippocampus bilaterally, the ventral posterior hippocampus unilaterally (left) and the ventral anterior hippocampus unilaterally (right). In young adults, the migraine group showed a significant inward displacement in the dorsal anterior hippocampus bilaterally, the ventral posterior hippocampus unilaterally (right) and the ventral anterior hippocampus unilaterally (right).

Discussion

Summary of results

The current investigation examined hippocampal structure in females with migraines across three critical developmental periods: childhood, adolescence, and young adulthood. While hippocampal structure has been separately investigated in children (Faria et al., 2015) and adult (Maleki et al., 2013; Hubbard et al., 2014; Liu et al., 2015) populations, this is among the first studies to include children and adults within the same investigation. Overall, results revealed a significant interaction effect of migraine diagnosis and developmental stage on hippocampal volume. Most strikingly, participants with migraines in both the childhood and adolescent groups displayed a similar pattern of decreased volume when compared to age-matched controls; however, the primary locality of the difference in shape shifted from the anterior to the posterior aspect of the hippocampus. The opposite effect (increased volume) was observed in the young adult group with migraines when compared to age-matched controls; however only the right hippocampus reached significance. Taken together, these results suggest that structural changes in the hippocampus in those with migraine are present and may involve an interaction of disease- and development-related processes.

The hippocampus and stress

The hippocampus is a structure that is particularly notable for its structural plasticity across the lifespan, including neurogenesis, synaptogenesis, and dendritic plasticity, in response to a range of both internal and external factors (McEwen, 2001). Glucocorticoids, among other mediators, are involved in this plasticity that can include increases in dendritic arborization, synapses and neurogenesis as well as decreases in volume of specific brain regions and circuit (Herman et al., 1995; Takahashi, 1998; Welberg and Seckl, 2001). Previous research has repeatedly demonstrated that both chronic stress and chronic pain can have profound effects on hippocampal structure and function (Duric and McCarson, 2006; Duric and McCarson, 2005). Alterations in hippocampal structure have been demonstrated in multiple chronic pain conditions (de Kruijf et al., 2016; Luchtmann et al., 2015; McCrae et al., 2015; Khan et al., 2014; Labus et al., 2014; Gianaros et al., 2007), notably including migraine (Maleki et al., 2013; Hubbard et al., 2014; Liu et al., 2015).

Fig. 3. Hippocampal shape differences, for both the left and right hippocampi, comparing migraineurs to healthy controls at each development stage (children, adolescents and young adults). Regions of significant vertex displacement are represented by the red-yellow color scale; the remaining non-significant surface is rendered in grey. Hippocampi are shown in both an anterior (dorsal surface) and posterior (ventral surface) view. D-dorsal, V-ventral, A-anterior, P-posterior, L-lateral, M-Medial, H-head, B-body, T-tail. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Hippocampus and migraine

Migraine, as both a neurological and chronic pain condition, is characterized by intermittent headache attacks that can be viewed as inciting repeated physiological and emotional stress (Borsook et al., 2012). Thus, in migraine, the hippocampus is particularly vulnerable to structural plasticity in response to both the physiological and emotional stress associated with migraine episodes. While chronic stress, in both animal models and adult human clinical studies, has predominantly been associated with hippocampal atrophy (i.e. general life stress (Sheline, 2003); major depression (Woon et al., 2010); and post-traumatic stress disorder (Finocchi and Strada, 2014) it is important to note that in the aforementioned studies of hippocampal volume in migraine (and other pain conditions) both increase and decrease in hippocampal structure have been observed.

Altered hippocampal volume across development in migraine. In the current study, hippocampal volumes were similarly decreased in children and adolescents with migraine. At present, several factors are thought to contribute to the evolution of migraine with age. For females with migraines, changes in ovarian hormones associated with reproductive events such as menarche, pregnancy, and menopause are associated with changes, both adaptive and maladaptive, in the expression of migraine. During adolescence, the predominance of migraine prevalence in females arises and an estimated 60% of these youth report migraines in relation to onset of menses, although only 6% report menstrual only migraine (Pavlović et al., 2015; Kroner-Herwig and Vath, 2009). In the current study, menarche (puberty) formed one of our developmental categorizations, however the impact of menarche on the expression of migraine in children aged 11–16 has been called into question by intra-individual longitudinal studies (LeResche et al., 2005), which have not revealed an increase in headache frequency after menarche (MacGregor et al., 2006). While there is a highly probable influence of gonadal hormones in menstrual migraine, particularly in later life (Epstein et al., 1975; Pavlović et al., 2016; Martin and Behbehani, 2006), their role in adolescence and non-menstrual related migraineurs remains speculative (Rao et al., 2010). Brain maturation (Bardou et al., 2013), duration of effects (Romeo et al., 2004), and group effects of estrogen/progesterone on neuronal plasticity and dendritic complexity (Hershey, 2012) may also play a role.

In contrast to the findings above, we found a significant interaction in hippocampal volumes between children and adolescents with migraine, compared with young adults. Our finding of an increased hippocampal volume in young-adult migraineurs is in accordance with previous neuroimaging studies of hippocampal structure in adults (Maleki et al., 2013; Hubbard et al., 2014; Liu et al., 2015). The pathophysiology of migraine in children and adolescents is presumed to be the same as in adults (Guidetti and Galli, 1998). Despite this assumption of a consistent central mechanism, there is a general consensus that the clinical manifestation of migraine may change over time, particularly in the transitionary phase of childhood to adolescence (Pakalnis and Gladstein, 2010). Increasingly, it is recognized that the etiology of migraine risk and the evolution of migraine expression in adolescents is likely multifactorial (Russo et al., 2016; Antonaci et al., 2014; Linet et al., 1989). Of particular note, migraine episodes may become more frequent and of longer duration, particularly for females (Bille, 1997) and a higher rate of remission and/or headache transformation occurs during this period (Guidetti et al., 1998; Kienbacher et al., 2006; Rhee, 2005). Adolescence is recognized as a period of both biological and psychosocial transition, with physically mature adolescents expected to assume higher levels of social responsibility into young adulthood, which may lead to increased psychological distress (Aegidius et al., 2011; Stanford et al., 2008). Psychosocial factors such as anxiety/depression, somatization and dysfunctional stress coping have arisen as important predictors of both increasing and high persistent levels of headache pain from early to late adolescence (Dunn et al., 2011; Isensee et al., 2016; Kelman, 2006). We did not observe any significant differences in clinical manifestation between development groups in our patient sample, apart from an expected difference in age of onset and disease duration. However, such trends in migraine presentation may only be evident in larger epidemiological based studies (McLaughlin et al., 2009).

Potential processes that contribute to alterations in hippocampal volume in migraine. The hippocampus is uniquely sensitive and vulnerable to changes in its activity due to stressful experiences as well as psychological trauma (e.g., abuse/neglect) due to its unique circuitry and involvement with glucocorticoids and excitatory amino acids along with other factors. Together, these processes promote both adaptive and maladaptive neuroplasticity as well as mediate damage when overused and dysregulated (McEwen, 2001; Brna et al., 2008), which may be relevant if migraine episodes can be considered as an example of a repeated stressor (Borsook et al., 2012; Maleki et al., 2012). Although speculative, the transition to increased hippocampal volume coinciding with development may be indicative of allostatic-related neuroplastic changes in relation to migraine-related stress (Roth-Isigkeit et al., 2005), as the deleterious effects of migraine on health-related quality of life increase with age (Nelson et al., 2021; Pinto et al., 2015). More recent investigations in other pediatric pain populations (i.e., musculoskeletal pain) have yielded a potential moderation effect between allostatic load and physical and psychological impairment (Fanselow and Dong, 2010), indicating the potential role of stress in impacting physical functioning in these populations. In support of this potential in the context of migraine, repeated exposure to stress has been observed to induce a volumetric enlargement of the ventral hippocampus (Sisk and Foster, 2004), similar to the vertex-based localization of volumetric change observed in this study. While the dorsal hippocampus primarily projects to the neocortex and is involved in memory and cognitive processing, the ventral hippocampus primary interacts with subcortical structures, including the amygdala and hypothalamus, and is involved in processing information related to emotion and homeostatic state (De Felice et al., 2010). Thus, in the dorsal–ventral axis of the hippocampus, the ventral component is uniquely placed to reflect allostatic-related morphological changes.

Limitations

There are several limitations in this study that must be acknowledged: (King et al., 2011). To begin, study aims were focused on females over the age of 7, which limits generalizability to more demographically varied populations. Generalizability was also limited due to lack of other demographic variables such as race/ethnicity and body-mass index. Small sample sizes and heterogeneity across groups also limits generalizability and interpretation of results. Relatedly, regarding the study design, while menarche represents a finite point for differentiation between childhood and adolescence, the distinction between adolescence and young adulthood is less precise. Adolescence culminates in both gonadal and behavioral maturation (Henry and Crawford, 2005) and in the absence of neuroendocrine measures the distinction was based on age: (Simons et al., 2015). Secondly, among the migraine patients, it may be that the developmental groups will have differential use of migraine pharmacotherapies, including triptans. This may be a potential confounder as these drugs may have modulatory effects on the central nervous system, although this appears to be primarily mediated via adaptions in the trigeminal ganglion (Anda et al., 2010). Nevertheless, individuals with migraine taking daily preventative medications were excluded in order to minimize this confound (Kashikar-Zuck et al., 2013). We only used an age segregation and not a biological separation at puberty. This issue would need to be further evaluated in future studies. Finally, analyses did not include compensation for multiple comparisons when developmental stages were evaluated. As such, results should be interpreted with caution.

Conclusions

This is the first study to examine hippocampal structure in migraine among a cohort of both pediatric and adults, allowing for the comparison of hippocampal volume during this important transitionary stage in neurodevelopment. Hippocampal volume was found to have an interactional relationship with migraine and developmental stage. We hypothesized that this reflects structural remodeling of the hippocampus in response to the chronic, unpredictable stressful nature of migraine. As such, future studies exploring stress responses, particularly HPA axis reactivity and allostasis, in children and adolescents with migraine (and other pain conditions) may prove a fruitful avenue of research. For example, use of validated measures such as the Depression Anxiety Stress Scale (DASS (Fichtel and Larsson, 2001) may be a useful measure in future investigations, as stress, anxiety, and depression are well-known to be comorbid with migraine (Stensland et al., 2013). It is important to consider that migraine commonly first manifests during a time of rapid development-related neural reorganization, and that ideally longitudinal imaging data from several time points may be necessary to determine how normative and pathological development in the hippocampus (and other brain regions) may ultimately play a role in the progression of migraine. Investigation of additional health metrics alongside stress and pain such as obesity (i.e., BMI) will also be important in future research.

CRediT authorship contribution statement

Sophie L. Wilcox: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Writing – original draft. **Sarah Nelson:** Conceptualization, Funding acquisition, Validation, Visualization, Writing – original draft, Writing – review & editing. **Allison Ludwick:** Conceptualization, Data curation, Formal analysis, Writing – original draft. **Andrew M. Youssef:** Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Alyssa Lebel:** Data curation, Validation, Visualization, Writing – original draft, Writing – review & editing. **Lino Beccera:** Data curation, Validation, Visualization, Writing – original draft, Writing – review & editing. **Rami Burstein:** Data curation, Validation, Visualization, Writing – original draft, Writing – review & editing. **David Borsook:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank all of the volunteers and their families who participated in this study. We would also like to thank Adriana Johnson and Rosanna Veggeberg for all of their assistance with the pediatric and adult migraine programs.

Funding

National Institute of Neurological Disorders and Stroke at the National Institutes of Health (Grant Numbers: K24NS064050 and R01NS0750182 to DB), The Department of Anesthesiology, Perioperative and Pain Medicine's Trailblazer Award (to SLW), and The National Center for Complementary and Integrative Health (Grant Number: 1K23AT010643 to SN).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynpai.2023.100137.

References

[1] Aegidius, K.L., Zwart, J.A., Hagen, K., Dyb, G., Holmen, T.L., Stovner, L.J., 2011. Increased headache prevalence in female adolescents and adult women with early menarche. The Head-HUNT Studies. Eur. J. Neurol. 18 (2), 321–328.
[2] Anda, R., Tietjen, G., Schulman, E., Felitti, V., Croft, J., 2010. Adverse childhood experiences and frequent headaches in adults. Headache 50 (9), 1473–1481.
[3] Antonaci, F., Voiticovschi-Iosob, C., Di Stefano, A.L., Galli, F., Ozge, A., Balottin, U., 2014. The evolution of headache from childhood to adulthood: a review of the literature. J. Headache Pain 15, 15.
[4] Bardou, I., Brothers, H.M., Kaercher, R.M., Hopp, S.C., Wenk, G.L., 2013. Differential effects of duration and age on the consequences of neuroinflammation in the hippocampus. Neurobiol. Aging 34 (10), 2293–2301.
[5] Bille, B., 1997. A 40-year follow-up of school children with migraine. Cephalalgia Int. J. Headache 17 (4), 488–491 discussion 7.
[6] Boccardi, M., Bocchetta, M., Apostolova, L.G., Barnes, J., Bartzokis, G., Corbetta, G., DeCarli, C., deToledo-Morrell, L., Firbank, M., Ganzola, R., Gerritsen, L., Henneman, W., Killiany, R.J., Malykhin, N., Pasqualetti, P., Pruessner, J.C., Redolfi, A., Robitaille, N., Soininen, H., Tolomeo, D., Wang, L., Watson, C., Wolf, H., Duvernoy, H., Duchesne, S., Jack, C.R., Frisoni, G.B., 2015. Delphi definition of the EADC-ADNI Harmonized Protocol for hippocampal segmentation on magnetic resonance. Alzheimers Dement. 11 (2), 126–138.
[7] Borsook, D., Maleki, N., Becerra, L., McEwen, B., 2012. Understanding migraine through the lens of maladaptive stress responses: a model disease of allostatic load. Neuron 73 (2), 219–234.
[8] Brna, P., Gordon, K., Dooley, J., 2008. Canadian adolescents with migraine: impaired health-related quality of life. J. Child Neurol. 23 (1), 39–43.
[9] Carrion, V.G., Weems, C.F., Reiss, A.L., 2007. Stress predicts brain changes in children: a pilot longitudinal study on youth stress, posttraumatic stress disorder, and the hippocampus. Pediatrics 119 (3), 509–516.
[10] Chapman, C.R., Tuckett, R.P., Song, C.W., 2008. Pain and stress in a systems perspective: reciprocal neural, endocrine, and immune interactions. J. Pain Off. J. Am. Pain Soc. 9 (2), 122–145.
[11] Colon, E., Ludwick, A., Wilcox, S.L., Youssef, A.M., Danehy, A., Fair, D.A., Lebel, A. A., Burstein, R., Becerra, L., Borsook, D., 2019. Migraine in the young brain: adolescents vs. young adults. Front. Hum. Neurosci. 13.
[12] De Felice, M., Ossipov, M.H., Wang, R., Dussor, G., Lai, J., Meng, I.D., Chichorro, J., Andrews, J.S., Rakhit, S., Maddaford, S., Dodick, D., Porreca, F., 2010. Triptan-induced enhancement of neuronal nitric oxide synthase in trigeminal ganglion dural afferents underlies increased responsiveness to potential migraine triggers. Brain J. Neurol. 133 (8), 2475–2488.
[13] de Kruijf, M., Bos, D., Huygen, F.J.P.M., Niessen, W.J., Tiemeier, H., Hofman, A., Uitterlinden, A.G., Vernooij, M.W., Ikram, M.A., van Meurs, J.B.J., 2016. Structural brain alterations in community dwelling individuals with chronic joint pain 37 (3), 430–438.
[14] Dunn, K.M., Jordan, K.P., Mancl, L., Drangsholt, M.T., Le Resche, L., 2011. Trajectories of pain in adolescents: a prospective cohort study. Pain 152 (1), 66–73.
[15] Duric, V., McCarson, K.E., 2005. Hippocampal neurokinin-1 receptor and brain-derived neurotrophic factor gene expression is decreased in rat models of pain and stress. Neuroscience 133 (4), 999–1006.
[16] Duric, V., McCarson, K.E., 2006. Persistent pain produces stress-like alterations in hippocampal neurogenesis and gene expression. J. Pain 7 (8), 544–555.
[17] Epstein, M.T., Hockaday, J.M., Hockaday, T.D., 1975. Migraine and reporoductive hormones throughout the menstrual cycle. Lancet (Lond., Engl.) 1 (7906), 543–548.
[18] Fanselow, M.S., Dong, H.W., 2010. Are the dorsal and ventral hippocampus functionally distinct structures? Neuron 65 (1), 7–19.
[19] Faria, V., Erpelding, N., Lebel, A., Johnson, A., Wolff, R., Fair, D., Burstein, R., Becerra, L., Borsook, D., 2015. The migraine brain in transition: girls vs boys. Pain 156 (11), 2212–2221.
[20] Fichtel, Å., Larsson, B., 2001. Does relaxation treatment have differential effects on migraine and tension-type headache in adolescents? Headache J. Head Face Pain 41 (3), 290–296.
[21] Finocchi, C., Strada, L., 2014. Sex-related differences in migraine. Neurol. Sci. Off. J. Ital. Neurol. Soc. Ital. Soc. Clin. Neurophysiol. 35 (Suppl 1), 207–213.
[22] Frisoni, G.B., Jack, C.R., Bocchetta, M., Bauer, C., Frederiksen, K.S., Liu, Y., Preboske, G., Swihart, T., Blair, M., Cavedo, E., Grothe, M.J., Lanfredi, M., Martinez, O., Nishikawa, M., Portegies, M., Stoub, T., Ward, C., Apostolova, L.G., Ganzola, R., Wolf, D., Barkhof, F., Bartzokis, G., DeCarli, C., Csernansky, J.G., deToledo-Morrell, L., Geerlings, M.I., Kaye, J., Killiany, R.J., Lehéricy, S., Matsuda, H., O'Brien, J., Silbert, L.C., Scheltens, P., Soininen, H., Teipel, S., Waldemar, G., Fellgiebel, A., Barnes, J., Firbank, M., Gerritsen, L., Henneman, W., Malykhin, N., Pruessner, J.C., Wang, L., Watson, C., Wolf, H., deLeon, M., Pantel, J., Ferrari, C., Bosco, P., Pasqualetti, P., Duchesne, S., Duvernoy, H., Boccardi, M., Albert, M.S., Bennet, D., Camicioli, R., Collins, D.L., Dubois, B., Hampel, H., denHeijer, T., Hock, C., Jagust, W., Launer, L., Maller, J.J., Mueller, S., Sachdev, P., Simmons, A., Thompson, P.M., Visser, P.-J., Wahlund, L.-O., Weiner, M.W., Winblad, B., 2015. The EADC-ADNI Harmonized Protocol for

manual hippocampal segmentation on magnetic resonance: evidence of validity. Alzheimers Dement. 11 (2), 111–125.
[23] Gianaros, P.J., Jennings, J.R., Sheu, L.K., Greer, P.J., Kuller, L.H., Matthews, K.A., 2007. Prospective reports of chronic life stress predict decreased grey matter volume in the hippocampus. Neuroimage 35 (2), 795–803.
[24] Guidetti, V., Galli, F., 1998. Evolution of headache in childhood and adolescence: an 8-year follow-up. Cephalalgia Int. J. Headache 18 (7), 449–454.
[25] Guidetti, V., Galli, F., Fabrizi, P., Giannantoni, A.S., Napoli, L., Bruni, O., Trillo, S., 1998. Headache and psychiatric comorbidity: clinical aspects and outcome in an 8-year follow-up study. Cephalalgia Int. J. Headache 18 (7), 455–462.
[26] Henry, J.D., Crawford, J.R., 2005. The short-form version of the Depression Anxiety Stress Scales (DASS-21): construct validity and normative data in a large non-clinical sample. Br. J. Clin. Psychol. 44 (2), 227–239.
[27] Herman, J.P., Adams, D., Prewitt, C., 1995. Regulatory changes in neuroendocrine stress-integrative circuitry produced by a variable stress paradigm. Neuroendocrinology 61 (2), 180–190.
[28] Hershey, A.D., 2012. Pediatric headache: update on recent research. Headache 52 (2), 327–332.
[29] Hershey, A.D., Winner, P., Kabbouche, M.A., Gladstein, J., Yonker, M., Lewis, D., Pearlman, E., Linder, S.L., Rothner, A.D., Powers, S.W., 2005. Use of the ICHD-II criteria in the diagnosis of pediatric migraine. Headache 45 (10), 1288–1297.
[30] Hubbard, C.S., Khan, S.A., Keaser, M.L., Mathur, V.A., Goyal, M., Seminowicz, D. A., 2014. Altered Brain structure and function correlate with disease severity and pain catastrophizing in migraine patients. eNeuro 1 (1).
[31] Huss, D., Derefinko, K., Milich, R., Farzam, F., Baumann, R., 2009. Examining the stress response and recovery among children with migraine. J. Pediatr. Psychol. 34 (7), 707–715.
[32] Isensee, C., Fernandez Castelao, C., Kroner-Herwig, B., 2016. Developmental trajectories of paediatric headache - sex-specific analyses and predictors. J. Headache Pain 17, 32.
[33] Isgor, C., Kabbaj, M., Akil, H., Watson, S.J., 2004. Delayed effects of chronic variable stress during peripubertal-juvenile period on hippocampal morphology and on cognitive and stress axis functions in rats. Hippocampus 14 (5), 636–648.
[34] Kashikar-Zuck, S., Zafar, M., Barnett, K.A., Aylward, B.S., Strotman, D., Slater, S.K., Allen, J.R., LeCates, S.L., Kabbouche, M.A., Ting, T.V., Hershey, A.D., Powers, S. W., 2013. Quality of life and emotional functioning in youth with chronic migraine and juvenile fibromyalgia. Clin. J. Pain 29 (12), 1066–1072.
[35] Kelman, L., 2006. Migraine changes with age: impact on migraine classification. Headache 46 (7), 1161–1171.
[36] Khan, S.A., Keaser, M.L., Meiller, T.F., Seminowicz, D.A., 2014. Altered structure and function in the hippocampus and medial prefrontal cortex in patients with burning mouth syndrome. Pain 155 (8), 1472–1480.
[37] Kienbacher, C., Wöber, C., Zesch, H.E., Hafferl-Gattermayer, A., Posch, M., Karwautz, A., Zormann, A., Berger, G., Zebenholzer, K., Konrad, A., Wöber-Bingöl, Ç., 2006. Clinical features, classification and prognosis of migraine and tension-type headache in children and adolescents: a long-term follow-up study. Cephalalgia Int. J. Headache 26 (7), 820–830.
[38] King, S., Chambers, C.T., Huguet, A., MacNevin, R.C., McGrath, P.J., Parker, L., et al., 2011. The epidemiology of chronic pain in children and adolescents revisited: a systematic review. Pain 152 (12), 2729–2738.
[39] Krogh, A.B., Larsson, B., Linde, M., 2015. Prevalence and disability of headache among Norwegian adolescents: a cross-sectional school-based study. Cephalalgia Int. J. Headache 35 (13), 1181–1191.
[40] Kroner-Herwig, B., Vath, N., 2009. Menarche in girls and headache–a longitudinal analysis. Headache 49 (6), 860–867.
[41] Labus, J.S., Dinov, I.D., Jiang, Z., Ashe-McNalley, C., Zamanyan, A., Shi, Y., Hong, J.-Y., Gupta, A., Tillisch, K., Ebrat, B., Hobel, S., Gutman, B.A., Joshi, S., Thompson, P.M., Toga, A.W., Mayer, E.A., 2014. Irritable bowel syndrome in female patients is associated with alterations in structural brain networks. Pain 155 (1), 137–149.
[42] Leistad, R.B., Stovner, L.J., White, L.R., Nilsen, K.B., Westgaard, R.H., Sand, T., 2007. Noradrenaline and cortisol changes in response to low-grade cognitive stress differ in migraine and tension-type headache. J. Headache Pain 8 (3), 157–166.
[43] LeResche, L., Mancl, L.A., Drangsholt, M.T., Saunders, K., Von Korff, M., 2005. Relationship of pain and symptoms to pubertal development in adolescents. Pain 118 (1–2), 201–209.
[44] Linet, M.S., Stewart, W.F., Celentano, D.D., Ziegler, D., Sprecher, M., 1989. An epidemiologic study of headache among adolescents and young adults. JAMA 261 (15), 2211–2216.
[45] Lipton, R.B., Bigal, M.E., 2005. Migraine: epidemiology, impact, and risk factors for progression. Headache 45 (Suppl 1), S3–s13.
[46] Liu, M.-G., Chen, J., 2009. Roles of the hippocampal formation in pain information processing. Neurosci. Bull. 25 (5), 237–266.
[47] Liu, J., Lan, L., Mu, J., Zhao, L., Yuan, K., Zhang, Y.i., Huang, L., Liang, F., Tian, J., 2015. Genetic contribution of catechol-O-methyltransferase in hippocampal structural and functional changes of female migraine sufferers. Hum. Brain Mapp. 36 (5), 1782–1795.
[48] Lobo, J.J., Ayoub, L.J., Moayedi, M., Linnstaedt, S.D., 2022. Hippocampal volume, FKBP5 genetic risk alleles, and childhood trauma interact to increase vulnerability to chronic multisite musculoskeletal pain. Sci. Rep. 12 (1), 6511.
[49] Luchtmann, M., Baecke, S., Steinecke, Y., Bernarding, J., Tempelmann, C., Ragert, P., et al., 2015. Changes in gray matter volume after microsurgical lumbar discectomy: a longitudinal analysis. Front. Hum. Neurosci. 9, 12.
[50] MacGregor, E.A., Frith, A., Ellis, J., Aspinall, L., Hackshaw, A., 2006. Incidence of migraine relative to menstrual cycle phases of rising and falling estrogen. Neurology 67 (12), 2154–2158.
[51] Maleki, N., Bernstein, C., Napadow, V., Field, A., 2016. Migraine and puberty: potential susceptible brain sites. Semin. Pediatr. Neurol. 23 (1), 53–59.
[52] Maleki, N., Becerra, L., Borsook, D., 2012. Migraine: maladaptive brain responses to stress. Headache 52 (Suppl 2), 102–106.
[53] Maleki, N., Becerra, L., Brawn, J., McEwen, B., Burstein, R., Borsook, D., 2013. Common hippocampal structural and functional changes in migraine. Brain Struct. Funct. 218 (4), 903–912.
[54] Martin, V.T., Behbehani, M., 2006. Ovarian hormones and migraine headache: understanding mechanisms and pathogenesis–part 2. Headache 46 (3), 365–386.
[55] McCrae, C.S., O'Shea, A.M., Boissoneault, J., Vatthauer, K.E., Robinson, M.E., Staud, R., et al., 2015. Fibromyalgia patients have reduced hippocampal volume compared with healthy controls. J. Pain Res. 8, 47–52.
[56] McEwen, B.S., 2001. Plasticity of the hippocampus: adaptation to chronic stress and allostatic load. Ann. N. Y. Acad. Sci. 933, 265–277.
[57] McLaughlin, K.J., Baran, S.E., Conrad, C.D., 2009. Chronic stress- and sex-specific neuromorphological and functional changes in limbic structures. Mol. Neurobiol. 40 (2), 166–182.
[58] Mutso, A.A., Radzicki, D., Baliki, M.N., Huang, L., Banisadr, G., Centeno, M.V., Radulovic, J., Martina, M., Miller, R.J., Apkarian, A.V., 2012. Abnormalities in hippocampal functioning with persistent pain. J. Neurosci. 32 (17), 5747–5756.
[59] Nelson, S., Bento, S., Enlow, M.B., 2021. Biomarkers of allostatic load as correlates of impairment in youth with chronic pain: an initial investigation. Children 8 (8), 709.
[60] Pakalnis, A., Gladstein, J., 2010. Headaches and hormones. Semin. Pediatr. Neurol. 17 (2), 100–104.
[61] Patenaude, B., Smith, S.M., Kennedy, D.N., Jenkinson, M., 2011. A Bayesian model of shape and appearance for subcortical brain segmentation. Neuroimage 56 (3), 907–922.
[62] Pavlović, J.M., Stewart, W.F., Bruce, C.A., Gorman, J.A., Sun, H., Buse, D.C., Lipton, R.B., 2015. Burden of migraine related to menses: results from the AMPP study. J. Headache Pain 16 (1).
[63] Pavlović, J.M., Allshouse, A.A., Santoro, N.F., Crawford, S.L., Thurston, R.C., Neal-Perry, G.S., Lipton, R.B., Derby, C.A., 2016. Sex hormones in women with and without migraine: evidence of migraine-specific hormone profiles. Neurology 87 (1), 49–56.
[64] Pinto, V., Costa, J.C., Morgado, P., Mota, C., Miranda, A., Bravo, F.V., Oliveira, T. G., Cerqueira, J.J., Sousa, N., 2015. Differential impact of chronic stress along the hippocampal dorsal-ventral axis. Brain Struct. Funct. 220 (2), 1205–1212.
[65] Rao, H., Betancourt, L., Giannetta, J.M., Brodsky, N.L., Korczykowski, M., Avants, B.B., Gee, J.C., Wang, J., Hurt, H., Detre, J.A., Farah, M.J., 2010. Early parental care is important for hippocampal maturation: evidence from brain morphology in humans. Neuroimage 49 (1), 1144–1150.
[66] Rhee, H., 2005. Relationships between physical symptoms and pubertal development. J. Pediatric Health Care Off. Publ. Natl. Assoc. Pediatric Nurse Assoc. Pract. 19 (2), 95–103.
[67] Romeo, R.D., Waters, E.M., McEwen, B.S., 2004. Steroid-induced hippocampal synaptic plasticity: sex differences and similarities. Neuron Glia Biol. 1 (3), 219–229.
[68] Roth-Isigkeit, A., Thyen, U., Stoven, H., Schwarzenberger, J., Schmucker, P., 2005. Pain among children and adolescents: restrictions in daily living and triggering factors. Pediatrics 115 (2), e152–e162.
[69] Russo, A., Bruno, A., Trojsi, F., Tessitore, A., Tedeschi, G., 2016. Lifestyle factors and migraine in childhood. Curr. Pain Headache Rep. 20 (2), 1–8.
[70] Satterthwaite, T.D., Vandekar, S., Wolf, D.H., Ruparel, K., Roalf, D.R., Jackson, C., Elliott, M.A., Bilker, W.B., Calkins, M.E., Prabhakaran, K., Davatzikos, C., Hakonarson, H., Gur, R.E., Gur, R.C., 2014. Sex differences in the effect of puberty on hippocampal morphology. J. Am. Acad. Child Adolesc. Psychiatry 53 (3), 341–350.e1.
[71] Sheline, Y.I., 2003. Neuroimaging studies of mood disorder effects on the brain. Biol. Psychiatry 54 (3), 338–352.
[72] Simons, L.E., Pielech, M., Cappucci, S., Lebel, A., 2015. Fear of pain in pediatric headache. Cephalalgia Int. J. Headache 35 (1), 36–44.
[73] Sisk, C.L., Foster, D.L., 2004. The neural basis of puberty and adolescence. Nat. Neurosci. 7 (10), 1040–1047.
[74] Stanford, E.A., Chambers, C.T., Biesanz, J.C., Chen, E., 2008. The frequency, trajectories and predictors of adolescent recurrent pain: a population-based approach. Pain 138 (1), 11–21.
[75] Stensland, S.Ø., Dyb, G., Thoresen, S., Wentzel-Larsen, T., Zwart, J.-A., 2013. Potentially traumatic interpersonal events, psychological distress and recurrent headache in a population-based cohort of adolescents: the HUNT study. BMJ Open 3 (7), e002997.
[76] Takahashi, L.K., 1998. Prenatal stress: consequences of glucocorticoids on hippocampal development and function. Int. J. Dev. Neurosci. 16 (3–4), 199–207.
[77] The International Classification of Headache Disorders, 2004. 2nd edition. Cephalalgia Int. J. Headache 24 (Suppl 1), 9–160.
[78] Welberg, L.A.M., Seckl, J.R., 2001. Prenatal stress, glucocorticoids and the programming of the brain. J. Neuroendocrinol. 13 (2), 113–128.
[79] Woon, F.L., Sood, S., Hedges, D.W., 2010. Hippocampal volume deficits associated with exposure to psychological trauma and posttraumatic stress disorder in adults: a meta-analysis. Prog. Neuropsychopharmacol. Biol. Psychiatry 34 (7), 1181–1188.
[80] Ziv, M., Tomer, R., Defrin, R., Hendler, T., 2010. Individual sensitivity to pain expectancy is related to differential activation of the hippocampus and amygdala. Hum. Brain Mapp. 31 (2), 326–338.