

ORIGINAL RESEARCH

Chronic Stroke Sensorimotor Impairment Is Related to Smaller Hippocampal Volumes: An ENIGMA Analysis

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BACKGROUND: Persistent sensorimotor impairments after stroke can negatively impact quality of life. The hippocampus is vulnerable to poststroke secondary degeneration and is involved in sensorimotor behavior but has not been widely studied within the context of poststroke upper-limb sensorimotor impairment. We investigated associations between non-lesioned hippocampal volume and upper limb sensorimotor impairment in people with chronic stroke, hypothesizing that smaller ipsilesional hippocampal volumes would be associated with greater sensorimotor impairment.

METHODS AND RESULTS: Cross-sectional T1-weighted magnetic resonance images of the brain were pooled from 357 participants with chronic stroke from 18 research cohorts of the ENIGMA (Enhancing Neuroimaging Genetics through Meta-Analysis) Stroke Recovery Working Group. Sensorimotor impairment was estimated from the FMA-UE (Fugl-Meyer Assessment of Upper Extremity). Robust mixed-effects linear models were used to test associations between poststroke sensorimotor impairment and hippocampal volumes (ipsilesional and contralesional separately; Bonferroni-corrected, $P < 0.025$), controlling for age, sex, lesion volume, and lesioned hemisphere. In exploratory analyses, we tested for a sensorimotor impairment and sex interaction and relationships between lesion volume, sensorimotor damage, and hippocampal volume. Greater sensorimotor impairment was significantly associated with ipsilesional ($P = 0.005$; $\beta = 0.16$) but not contralesional ($P = 0.96$; $\beta = 0.003$) hippocampal volume, independent of lesion volume and other covariates ($P = 0.001$; $\beta = 0.26$). Women showed progressively worsening sensorimotor impairment with smaller ipsilesional ($P = 0.008$; $\beta = -0.26$) and contralesional ($P = 0.006$; $\beta = -0.27$) hippocampal volumes compared with men. Hippocampal volume was associated with lesion size ($P < 0.001$; $\beta = -0.21$) and extent of sensorimotor damage ($P = 0.003$; $\beta = -0.15$).

CONCLUSIONS: The present study identifies novel associations between chronic poststroke sensorimotor impairment and ipsilesional hippocampal volume that are not caused by lesion size and may be stronger in women.

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Preprint posted on BioRxiv October 28, 2021. doi: <https://doi.org/10.1101/2021.10.26.465924>

Supplemental Material for this article is available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.025109>

For Sources of Funding and Disclosures, see page 12.

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Key Words: hippocampus ■ MRI ■ sensorimotor impairment ■ stroke

CLINICAL PERSPECTIVE

What Is New?

- In this study, we report a novel association between more severe sensorimotor impairment and smaller ipsilesional hippocampal volume in patients with chronic stroke, which is not caused by lesion size or lesion damage to sensorimotor-specific regions, and which may be stronger in women than in men.

What Are the Clinical Implications?

- These findings are of clinical interest because they provide initial evidence linking the integrity of the non-lesioned hippocampus (a key region of the limbic system associated with cognition and mood) to poststroke sensorimotor outcomes. This result provides support for holistic therapeutic approaches that are applicable to multiple domains of well-being.

Nonstandard Abbreviations and Acronyms

ENIGMA	Enhancing NeuroImaging Genetics through Meta-Analysis
FMA-UE	Fugl-Meyer Assessment of Upper Extremity
SD	spreading depression

Sensorimotor impairments are a major burden of disease for stroke survivors.¹ To help clinicians, caregivers, and patients make informed and effective rehabilitation treatment decisions, there is a critical need to identify biomarkers that accurately predict a patient's potential for sensorimotor recovery.^{2,3} Magnetic resonance imaging (MRI) studies of regional brain volumes suggest that secondary degeneration of adjacent or remote regions may contribute to sensorimotor impairment and could influence poststroke sensorimotor outcomes.^{4,5}

The hippocampus is a brain region that is particularly vulnerable to poststroke secondary degeneration. Both rodent⁶ and human⁷⁻⁹ stroke studies have shown evidence of damage within the hippocampus in the same hemisphere as an infarct (ipsilesional), but outside of the lesion itself. Using structural MRI, smaller ipsilesional hippocampal volumes in patients with stroke have been reported in comparison to healthy

controls,⁷⁻⁹ as well as smaller bilateral hippocampal volumes at the time of stroke¹⁰ and accelerated hippocampal atrophy observed most prominently 3 months after stroke.^{6,9} Studies have also reported magnetic resonance spectroscopy evidence of contralesional hippocampal neuronal loss⁸ and contralesional hippocampal atrophy measured with longitudinal MRI.⁹ Given that stroke-related infarctions of the hippocampus are uncommon,¹¹ poststroke hippocampal atrophy may be attributed to secondary degenerative mechanisms such as spreading depression (SD)⁶ or reduced connectivity to lesioned structures,¹¹ among others. However, the extent to which lesion volume relates to hippocampal damage remains unclear.

The hippocampus is widely known for its key role in memory, and this has led the field of stroke recovery research to primarily focus on the role of hippocampal damage in cognitive impairment.⁶⁻⁸ Although not typically considered a primary sensorimotor region, there is evidence that the hippocampus may also be involved in sensorimotor behavior. The hippocampus is densely connected to brain areas that play an important role in sensorimotor processing such as the thalamus and basal ganglia through the spinal-limbic pathway.¹² Reports of hippocampal activity during sensorimotor behavior such as sensorimotor integration,¹³ sensorimotor learning,¹⁴ and motor control¹⁴ suggest that the hippocampus plays a role in sensorimotor circuits. Sensorimotor task-related functional connectivity with the hippocampus has also been reported with the thalamus,¹⁵ sensorimotor cortex,¹⁴ and the supplementary motor area.¹⁶ However, the relationship between hippocampal structural integrity and poststroke upper-limb sensorimotor impairment remains unclear. Given the potential involvement of the hippocampus in sensorimotor circuits, hippocampal damage caused by secondary degeneration after stroke could further weaken sensorimotor circuits, leading to greater chronic sensorimotor impairment. Alternatively, damage to the thalamus, basal ganglia, sensorimotor cortex, or supplementary motor area, which are typically associated with greater sensorimotor impairment, may lead to downstream degeneration of the hippocampus through functional or structural connections.

Dementia studies¹⁷ and healthy aging¹⁸ research also suggest that hippocampal atrophy may differ by sex, because hippocampal atrophy has been found to accelerate in women after menopause. Estrogen levels may play a mediating role in these trends¹⁹ and have been associated with stroke severity and mortality.²⁰ Stroke-related outcomes including disability and quality of life are generally poorer in women than men,^{1,21}

although conclusive sex differences have not been reported in terms of poststroke sensorimotor impairment.²² As such, sex could moderate the relationship between sensorimotor impairment and hippocampal volume following a stroke. In particular, women may have smaller hippocampal volumes and worse sensorimotor impairment, potentially leading to stronger effect sizes compared with men.

In addition, associations between lesion size and hippocampal volume remain unclear. One study reports that larger lesion size is directly associated with smaller hippocampal volumes,⁷ while other studies report no clear relationship.^{6,8} Given this lack of consensus, we also investigated whether lesion size was independently associated with hippocampal volume, using a large sample of brain MRI scans with manually segmented stroke lesions.

The current study is a first step towards examining whether there is an association between the volume of the non-lesioned poststroke hippocampus and sensorimotor impairment using a large cross-sectional data set. In this study, we aimed to investigate the relationship between sensorimotor impairment and ipsilesional and contralesional hippocampal volumes (separately) in 357 participants with chronic stroke across 18 cohorts from the ENIGMA (Enhancing Neuroimaging Genetics through Meta-Analysis) Stroke Recovery Working Group.²³ Because of the heterogeneity of poststroke brain reorganization across individuals, large consortium-based multisite studies such as the ENIGMA Stroke Recovery Working Group are important for achieving large and diverse samples that can identify associations that may have otherwise been undetectable in a smaller single-site sample.²⁴ In addition, the diversity of data allows us to verify whether associations are maintained beyond a single cohort, improving the robustness and generalizability of research findings. First, we investigated associations between sensorimotor impairment and hippocampal volume, controlling for lesion size and additional covariates of age, sex, and lesioned hemisphere. The Fugl-Meyer Assessment of Upper Extremity (FMA-UE) was used as a measure of sensorimotor impairment of the paretic upper limb.²⁵ We hypothesized that greater poststroke sensorimotor impairment would be correlated with smaller ipsilesional but not contralesional hippocampal volume. We hypothesized, based on the involvement of the hippocampus in sensorimotor circuits, that the association between ipsilesional hippocampal volume and sensorimotor impairment would be independent of lesion size. Second, in an exploratory analysis, we tested to see whether sex had a moderating effect on the relationship between sensorimotor impairment and hippocampal volume. Because of more severe hippocampal vulnerability and poorer stroke outcome trends in women, we hypothesized that women would have a

stronger relationship between more severe sensorimotor impairment and smaller hippocampal volume than men. Given the lack of consensus in the literature regarding lesion size and hippocampal volume, we independently tested associations between lesion size and hippocampal volume, without the FMA-UE included in the model. We hypothesized that larger lesion size would be significantly associated with smaller ipsilesional but not contralesional hippocampal volumes. Finally, we also tested to see whether damage to sensorimotor regions specifically was associated with ipsilesional hippocampal volume. We hypothesized that greater damage to sensorimotor regions would be correlated with smaller ipsilesional hippocampal volumes, independent of lesion size.

METHODS

Data Availability

To protect the privacy of research participants, individual subject data used in this study are not available in a public repository. Participating research cohorts vary in public data-sharing restrictions as determined by the following: (1) ethical review board and consent documents; (2) national and transnational sharing laws; and (3) institutional processes that may require signed data transfer agreements for limited, predefined data use. However, data sharing is possible for new and participating ENIGMA Stroke Recovery Working Group members who agree to the consortium's ethical standards for data use and upon the submission of a secondary analysis plan for group review. Upon the approval of the proposed analysis plan, access to relevant data is provided contingent on local principal investigator approval, data availability, and compliance with supervening regulatory boards. Deidentified summary data as well as code used for this study can be made available upon reasonable request to the corresponding author.

ENIGMA Stroke Recovery Data Set

A subset of cross-sectional data from the ENIGMA Stroke Recovery Working Group database (available as of December 15, 2020) was used. Details of the ENIGMA Stroke Recovery procedures and methods are available in Liew and colleagues.²³ The data were derived from 18 research studies (cohorts) conducted at 10 different research institutes in 6 countries (Table 1). Informed consent was obtained from all subjects, and data were collected in compliance with each institution's local ethical review boards and in accordance with the Declaration of Helsinki.

ENIGMA Stroke Recovery participants with the following data were included: (1) high-resolution (1-mm isotropic) T1-weighted brain MRI (T1w) acquired with a

Table 1. Demographics for ENIGMA Stroke Recovery Working Group Participants Included in the Study by Cohort

Cohort	Total No. (women/men)	Median age (y) (IQR, min–max)	Median FMA-UE (IQR, min–max)	Median lesion size (cm ³) (IQR, min–max)
Cohort 1	39 (10/29)	61 (17, 31–80)	43 (16, 0–58)	6.1 (20.3, 0.04–120.8)
Cohort 2	12 (6/6)	69.5 (12, 39–85)	33 (27, 13–48)	28.3 (28.5, 4.2–137.4)
Cohort 3	15 (6/9)	61 (17, 33–85)	16 (13, 5–40)	21.1 (68.7, 0.6–182.2)
Cohort 4	19 (6/13)	44 (15, 30–68)	10 (11, 1–34)	35.8 (54.4, 4.5–313.5)
Cohort 5	28 (12/16)	64 (18, 44–81)	52 (33, 8–65)	1.9 (25.7, 0.1–237.7)
Cohort 6	10 (3/7)	61 (12.5, 49–72)	65 (3, 45–65)	1.4 (1.1, 0.5–9.1)
Cohort 7	14 (5/9)	58 (12, 45–69)	63 (14, 6–65)	2.0 (2.9, 0.04–6.9)
Cohort 8	11 (4/7)	56 (12, 45–74)	48 (15, 25–55)	35.8 (50.2, 0.7–103.9)
Cohort 9	11 (3/8)	59 (3, 45–68)	38 (18, 15–49)	2.6 (21.7, 0.7–53.7)
Cohort 10	8 (4/4)	58 (8, 46–73)	48 (16, 35–59)	28.4 (43.2, 0.4–59)
Cohort 11	22 (6/16)	61.5 (11, 23–75)	49 (22, 23–64)	5.6 (41.5, 0.4–201.4)
Cohort 12	13 (4/9)	57 (13, 32–80)	54 (15, 38–63)	4.8 (18.2, 0.3–98)
Cohort 13	12 (4/8)	66 (16, 31–83)	51 (26, 19–62)	4.4 (37.6, 0.2–107.5)
Cohort 14	29 (18/11)	50 (15, 25–79)	41 (13, 24–53)	12.1 (28.6, 0.1–143.6)
Cohort 15	10 (3/7)	61.5 (11, 42–76)	29 (16, 11–60)	9.1 (23.4, 3–186.1)
Cohort 16	40 (14/26)	66.5 (11, 43–93)	47 (30, 4–65)	9.2 (26.1, 0.5–111.8)
Cohort 17	36 (15/21)	70 (14, 37–80)	53 (27, 8–65)	7.6 (29.3, 0.3–188.4)
Cohort 18	28 (12/16)	64 (14, 34–85)	27 (5, 14–34)	5 (29.4, 0.7–136.9)
Total	357 (135/222)	61 (18, 23–93)	41 (28, 0–65)	7.6 (33.4, 0.04–313.5)

Total sample size (N), number of women and men, and information about age (years), Fugl-Meyer Assessment of Upper Extremity (FMA-UE), and raw lesion size in cubic centimeters (cm³) are listed. For more information regarding cohort demographics by sex, see Tables S1 and S2. ENIGMA indicates Enhancing Neuroimaging Genetics through Meta-Analysis; and IQR, interquartile range.

3T MRI scanner; (2) Fugl-Meyer Assessment of Upper Extremity score (FMA-UE; acquired on a scale from 0 to 66: 0=severe sensorimotor impairment, 66=no sensorimotor impairment); (3) age; and (4) sex. Because we were interested in studying effects of secondary degeneration of the hippocampus, we only included participants with chronic stroke (defined as data acquired at least 180 days poststroke²⁶). Behavioral data were collected within ≈72 hours of the MRI. Exclusion criteria included site-reported bilateral, brainstem, or cerebellar lesions; participants with no identifiable lesions; and participants with no sensorimotor impairment (FMA-UE=66). In addition, each hippocampus was visually inspected with lesion masks overlaid, and any brains with hippocampal lesions were excluded. The total initial sample size was N=357 (age: median=61 years, interquartile range=18, range=23–93; FMA-UE: median=41, interquartile range=28, range=0–65; 135 women and 222 men) (Table 1).

MRI Data Analysis

Hippodeep, an automated convolutional neural network-based hippocampal segmentation algorithm, was used to segment ipsilesional and contralesional hippocampal volumes as well as estimated total head size from the T1-weighted MRI scan.²⁷ Hippodeep was previously found to be the most robust out of the freely

available methods for segmenting the hippocampus in people with stroke pathology.²⁸ Hippocampal segmentations were visually inspected according to previously described protocols.^{23,28} Any segmentations that were not properly segmented were marked as failed and excluded from the analysis. This resulted in different sample sizes for the ipsilesional and contralesional analyses. More information on demographics of samples after quality control can be found in Tables S1 and S2. We performed a supplemental analysis using only participants with hippocampal segmentations that passed quality control for both ipsilesional and contralesional hippocampi and confirmed that differences in sample sizes did not significantly influence the results (Tables S3 through S6). To account for differences in head size, hippocampal volume was normalized for head size by taking the ratio of hippocampal volume to head size for each participant and multiplying it by the average head size across the sample, as done in previous studies of poststroke hippocampal volume.^{7,8}

Manually Segmented Lesions

Lesions were manually segmented on the T1w MRI by B.L., M.D., J.S., A.Z.P., and S.-L.L. according to an updated version of the Anatomical Tracings of Lesions After Stroke (ATLAS) protocol.²⁹ Briefly, brain lesions were identified, and masks were manually drawn on

each individual brain in native space using ITK-Snap.³⁰ Each lesion was checked for quality by at least 2 different tracers. An expert neuroradiologist (G.B.) was also consulted to ensure lesion segmentation accuracy. The ATLAS protocol for manually tracing stroke lesions has been technically validated, with high inter- and intrarater reliability. More details on the criteria used to manually trace lesions, including links to the lesion-tracing protocol, can be found in Liew and colleagues.²⁹ The sample includes 81 participants with cortical lesions, 100 participants with subcortical lesions, and 176 participants with mixed cortical and subcortical lesions. Although all participants were listed by the providing research sites as having unilateral lesions, additional secondary lesions were discovered in 100 participants during manual tracing, which were likely silent, subclinical, and/or prior strokes. Secondary lesions were found in both hemispheres, the brainstem, and the cerebellum, and ranged in size. For this article, we refer to the primary lesioned hemisphere as the lesioned hemisphere noted by the research site. We also performed follow-up analyses excluding participants with any identified secondary lesions (Figure S1), which did not significantly impact results (Tables S7 and S8). Lesion probability maps were generated by nonlinearly normalizing lesion masks and registering them to the MNI-152 template (Figure 1).

Finally, lesion volume was calculated by summing the voxels within each lesion mask. Lesion size was also normalized for head size as previously described for hippocampal volume in MRI Data Analysis Section. Lesion size was then log transformed to normalize the distribution of the data.

Sensorimotor Damage

Sensorimotor damage was estimated by calculating the percentage of lesion voxels that overlapped with the sensorimotor cortex, supplementary motor cortex, thalamus, or the basal ganglia, as calculated using the open-source software Pipeline for Analyzing Lesions after Stroke (PALS³¹). Briefly, T1w images and their accompanying lesion masks were nonlinearly registered to the MNI-152 template. Regions of interest reflecting the sensorimotor cortex, supplementary motor cortex, thalamus, and basal ganglia were identified using the Desikan-Killiany Atlas.³² Sensorimotor cortex and supplementary motor cortex were estimated using the pre- and postcentral gyrus. The basal ganglia were estimated using the caudate, pallidum, putamen, and nucleus accumbens. The number of lesioned voxels in the sensorimotor cortex, supplementary motor cortex, thalamus, and basal ganglia was summed and divided by the sum of the size of each sensorimotor region. This value was then multiplied by 100 to create a percent of lesion overlap with sensorimotor regions, reflecting sensorimotor damage.

Statistical Analysis

Hippocampal Volume and Sensorimotor Impairment

We first tested our primary hypothesis that more severe poststroke sensorimotor impairment is correlated with smaller ipsilesional but not contralesional hippocampal volumes by performing robust mixed-effects linear regressions with hippocampal volume as the dependent variable (see *Model 1*). Sensorimotor impairment

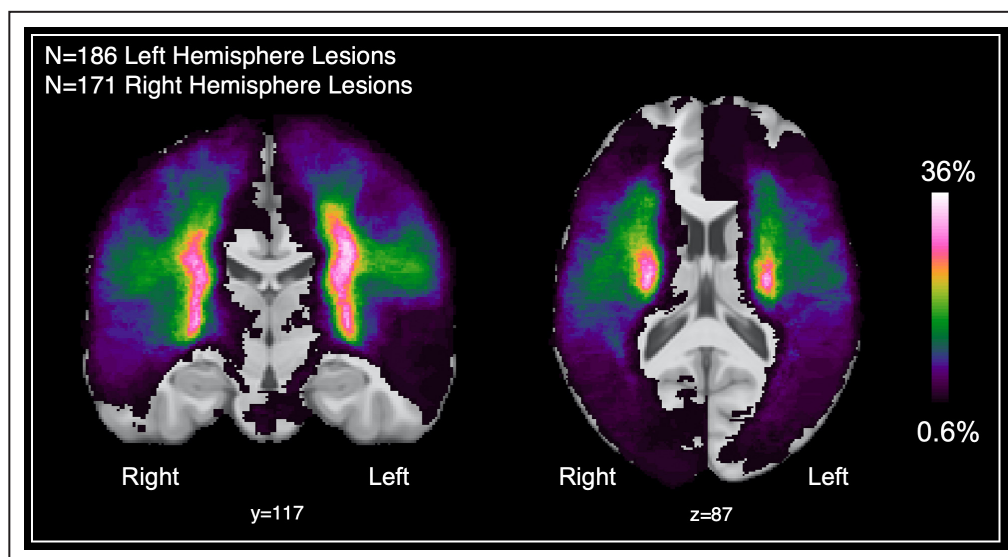


Figure 1. Lesion density maps for primary lesions from participants with cohort-reported left and right hemisphere lesions are overlaid on a coronal (left) and axial (right) slice of the Montreal Neurological Institute (MNI) MNI-152 template.

Lesioned hemisphere refers to the primary lesion, as reported by the research cohort. The color bar refers to the percentage of overlapping lesions across participants.

was measured using the FMA-UE.³³ Sex (coded as a binary variable: women=0, men=1), age, and lesioned hemisphere (coded as binary variable: left hemisphere lesion=0.5, right hemisphere lesion=1.5) were included in the model as fixed effects and cohort was included in the model as a random effect (Model 1):

$$\begin{aligned} \text{Hippocampus} &\sim \text{FMA} - \text{UE} \\ &+ \text{Sex} + \text{Age} + \text{Lesioned hemisphere} \\ &+ \text{random}(\text{Cohort}) \end{aligned} \quad (1)$$

Next, we tested our exploratory hypothesis that sex may have a moderating effect on the relationship between sensorimotor impairment and hippocampal volume by including an FMA-UE \times Sex interaction covariate as a fixed effect (Model 2):

$$\begin{aligned} \text{Hippocampus} &\sim \text{FMA} - \text{UE} \\ &+ \text{Sex} + \text{FMA} - \text{UE} \times \text{Sex} \\ &+ \text{Age} + \text{Lesioned hemisphere} \\ &+ \text{random}(\text{Cohort}) \end{aligned} \quad (2)$$

Sex differences in sensorimotor impairment, lesion size, and age were tested using an independent *t* test.

Finally, we tested our hypothesis that sensorimotor impairment is independently associated with hippocampal volume regardless of lesion size by including lesion size as a fixed covariate (Model 3):

Table 2. Summary Statistics From Robust Mixed-Effects Linear Regression to Test Associations Between Ipsilesional Hippocampal Volume and Sensorimotor Impairment and Contralateral Hippocampal Volume and Sensorimotor Impairment When Including a Sensorimotor Impairment and Sex Interaction

Hippocampus~FMA-UE \times Sex+FMA-UE+sex+lesioned hemisphere+age+random (cohort)			
Covariates	β (CI)	SE	<i>P</i> value
Ipsilesional hippocampal volume (N=336; $R^2=0.30$)			
FMA-UE*	0.31 (0.15 to 0.46)*	0.08*	<0.001*
FMA-UE \times sex*	-0.26 (-0.46 to -0.07)*	0.10*	0.009*
Sex*	-0.53 (-0.73 to -0.33)*	0.10*	<0.001*
Lesioned hemisphere	0.17 (-0.03 to 0.37)	0.10	0.09
Age*	-0.32 (-0.42 to -0.22)*	0.05*	<0.001*
Contralateral hippocampal volume (N=349; $R^2=0.32$)			
FMA-UE	0.16 (0.01 to 0.31)	0.08	0.04
FMA-UE \times sex*	-0.27 (-0.46 to -0.08)*	0.10*	0.006*
Sex*	-0.51 (-0.70 to -0.32)*	0.10*	<0.001*
Lesioned hemisphere*	-0.35 (-0.54 to -0.16)*	0.10*	<0.001*
Age*	-0.41 (-0.51 to -0.32)*	0.05*	<0.001*

The full model as well as the sample size (N), conditional R^2 , β coefficient (β) with 95% CI, SE, and uncorrected *P* value for all fixed-effect covariates are reported. FMA-UE indicates Fugl-Meyer Assessment of Upper Extremity.

*Significant covariates.

$$\begin{aligned} \text{Hippocampus} &\sim \text{Lesion size} + \text{FMA} - \text{UE} \\ &+ \text{Sex} + \text{FMA} - \text{UE} \times \text{Sex} \\ &+ \text{Age} + \text{Lesioned hemisphere} \\ &+ \text{random}(\text{Cohort}) \end{aligned} \quad (3)$$

Associations Between Lesion Size and Hippocampal Volume

To investigate associations between lesion size and hippocampal volume, regardless of sensorimotor impairment, we performed a robust mixed-effects regression with ipsilesional and contralateral hippocampal volume as dependent variables with lesion size, age, sex, and lesioned hemisphere as fixed effects, and cohort as a random effect (Model 4):

$$\begin{aligned} \text{Hippocampus} &\sim \text{Lesion size} \\ &+ \text{Sex} + \text{Age} + \text{Lesioned hemisphere} \\ &+ \text{random}(\text{Cohort}) \end{aligned} \quad (4)$$

Associations Between Sensorimotor Damage and Hippocampal Volume

We investigated our hypothesis that greater sensorimotor-specific lesion damage would be associated with smaller ipsilesional hippocampal volumes with a robust mixed-effects regression with ipsilesional hippocampal volume as the dependent variable and

Table 3. Summary Statistics From Robust Mixed-Effects Linear Regression to Test Associations Between Ipsilesional Hippocampal Volume and Sensorimotor Impairment and Contralateral Hippocampal Volume and Sensorimotor Impairment When Including Lesion Size as a Covariate

Hippocampus~lesion size+FMA-UE \times Sex+FMA-UE+sex+lesioned hemisphere+age+random (cohort)			
Covariates	β (CI)	SE	<i>P</i> value
Ipsilesional hippocampal volume (N=336; $R^2=0.33$)			
FMA-UE*	0.26 (0.10 to 0.41)*	0.08*	0.001*
FMA-UE \times sex*	-0.26 (-0.45 to -0.07)*	0.10*	0.008*
Lesion size*	-0.19 (-0.29 to -0.09)*	0.05*	<0.001*
Sex*	-0.58 (-0.78 to -0.39)*	0.10*	<0.001*
Lesioned hemisphere	0.17 (-0.03 to 0.36)	0.10	0.09
Age*	-0.36 (-0.46 to -0.26)*	0.05*	<0.001*
Contralateral hippocampal volume (N=349; $R^2=0.32$)			
FMA-UE	0.15 (0.00 to 0.30)	0.08	0.05
FMA-UE \times sex*	-0.27 (-0.46 to -0.08)*	0.10*	0.006*
Lesion size	-0.03 (-0.13 to 0.07)	0.05	0.58
Sex*	-0.52 (-0.71 to -0.33)*	0.10*	<0.001*
Lesioned hemisphere*	-0.35 (-0.54 to -0.16)*	0.10*	<0.001*
Age*	-0.42 (-0.52 to -0.32)*	0.05*	<0.001*

The full model as well as the sample size (N), conditional R^2 , β coefficient (β) with 95% CI, SE, and uncorrected *P* value for all fixed-effect covariates are reported. FMA-UE indicates Fugl-Meyer Assessment of Upper Extremity.

*Significant covariates.

percent of sensorimotor damage, age, sex, and lesioned hemisphere as fixed effects, and cohort as a random effect (Model 5):

$$\begin{aligned} & \text{Hippocampus} \sim \text{Sensorimotor damage} \\ & + \text{Sex} + \text{Age} + \text{Lesioned hemisphere} \\ & + \text{random}(\text{Cohort}) \end{aligned} \quad (5)$$

We also tested the hypothesis that sensorimotor damage is independently associated with hippocampal volume regardless of lesion size by including lesion size as a fixed covariate (Model 6):

$$\begin{aligned} & \text{Hippocampus} \sim \text{Sensorimotor damage} \\ & + \text{Lesion size} + \text{Sex} + \text{Age} \\ & + \text{Lesioned hemisphere} \\ & + \text{random}(\text{Cohort}) \end{aligned} \quad (6)$$

Statistical Tools

All statistical analyses were performed in R (version 4.0.2³³). The Mahalanobis distance was used to detect multivariate outliers,³⁴ which were then removed from the analyses (Data S1). All continuous measures were normalized using the *scale* function in R and analyzed as z-scores to

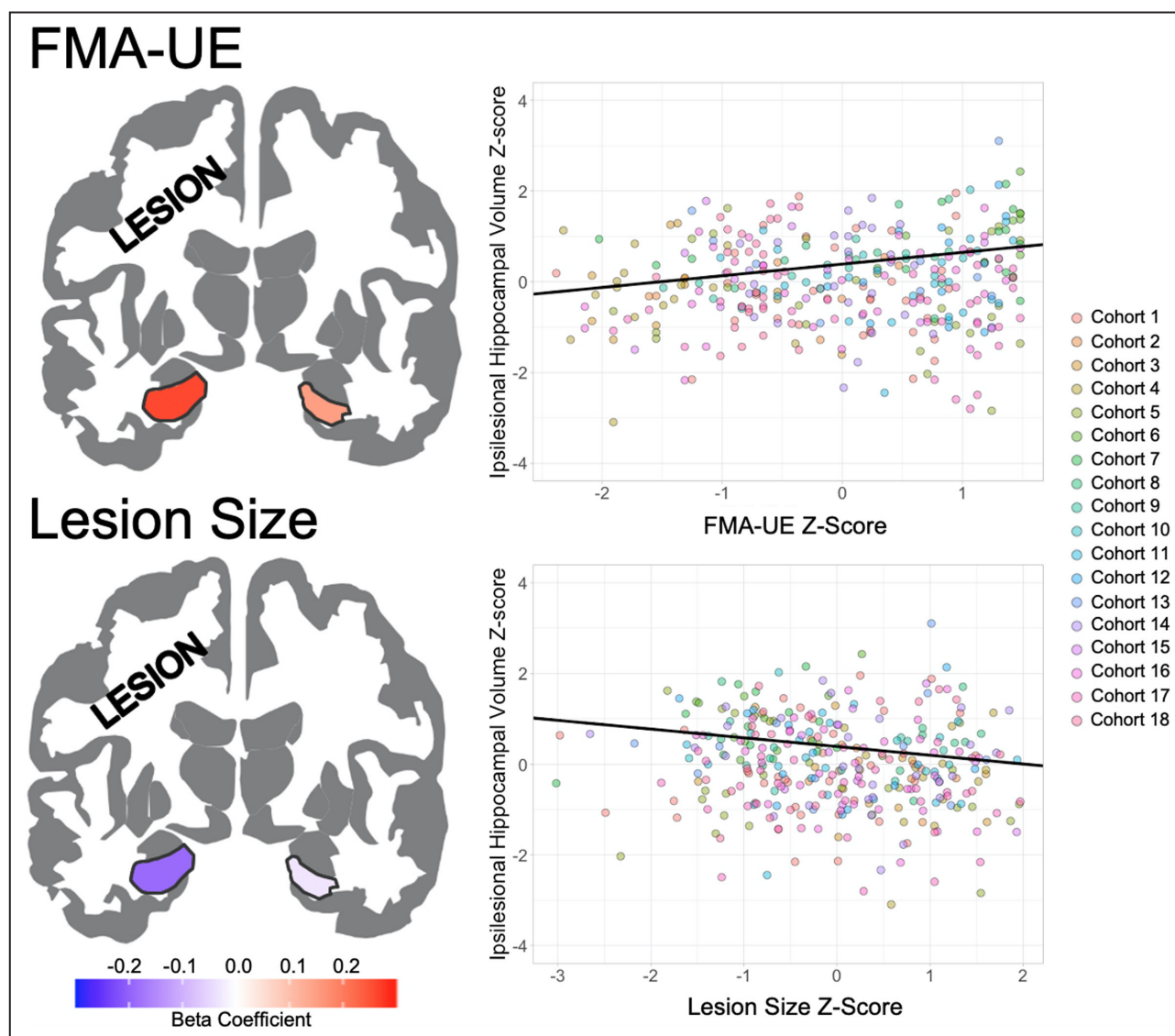


Figure 2. Effect sizes (standardized β values) for ipsilesional and contralesional hippocampi are mapped onto a template for associations between hippocampal volumes and sensorimotor impairment (top left) and lesion size (bottom left), with warmer colors representing stronger positive associations.

Trend lines (black line) are plotted for the association between ipsilesional hippocampal volume z-scores with Fugl-Meyer Assessment of Upper Extremity (FMA-UE) z-scores (top right) and lesion size z-scores (bottom right). Scatterplot points are colored by research cohort.

calculate standardized β coefficients. All mixed-effects regressions were initially run as linear mixed-effects regressions (*lmer* function from *nlme* package). To ensure that there was no redundancy in the included independent variables, collinearity for variables in every model tested was ruled out (variance inflation factor ≤ 2.5 ; Tables S9 and S10). Regression assumptions of linearity, normality of the residuals, and homogeneity of the residual variance were tested by visually inspecting residuals versus fits plots as well as qq-plots. After detecting influential observations using Cook's distance in each analysis,³⁵ the analyses were repeated using robust mixed-effects regression. Robust mixed-effects regression (*rlmer* from the *robustlmm* package) avoids excluding data by reducing the weight of influential observations.³⁶ We therefore report the results of the robust mixed-effects regression. For all analyses, β coefficients for the factor of interest and CIs (β [CI]), SE, and uncorrected P values are reported. For each analysis, a Bonferroni correction was applied for 2 comparisons (ipsilesional, contralesional; corrected

$P < 0.025$). Effect sizes were mapped onto a template of the hippocampus to visualize the results using *ggseg*.³⁷

RESULTS

Hippocampal Volume and Sensorimotor Impairment

Greater sensorimotor impairment was significantly associated with smaller ipsilesional ($\beta = 0.16$, $P = 0.005$, $R^2 = 0.27$) but not contralesional ($\beta = 0.003$, $P = 0.96$, $R^2 = 0.29$) hippocampal volume after adjusting for age, sex, lesioned hemisphere, and cohort (Table S11). When including FMA-UE \times Sex interaction as a covariate, we observed a better model fit and an increase in effect size for the association between sensorimotor impairment and ipsilesional hippocampal volume ($\beta = 0.31$, $P < 0.001$, $R^2 = 0.30$; Table 2). Furthermore, FMA-UE remained independently associated with ipsilesional hippocampal volume after including lesion size in the model ($\beta = 0.26$, $P = 0.001$, $R^2 = 0.33$; Table 3, Figure 2). This association

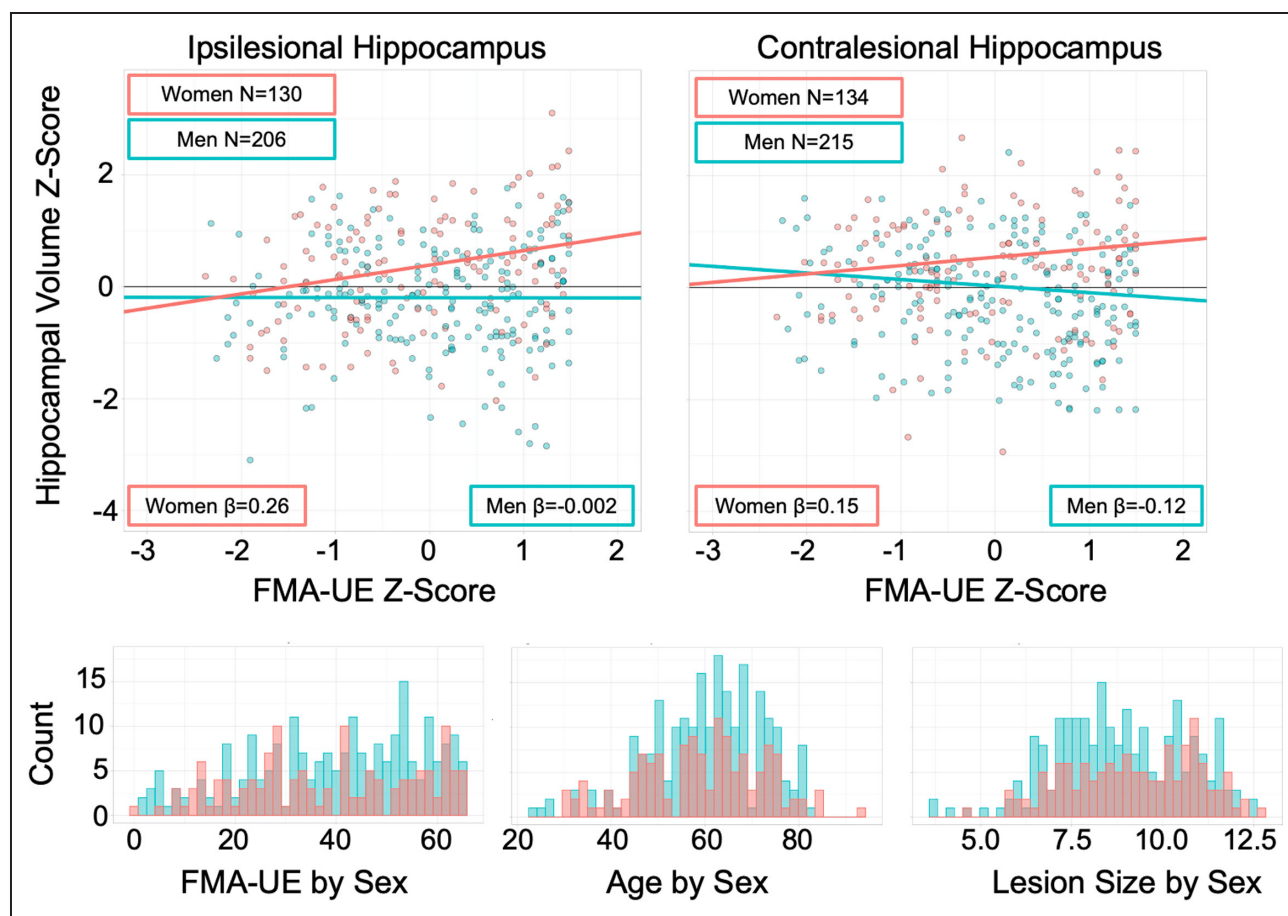


Figure 3. Trend lines are plotted for the association between Fugl-Meyer Assessment of Upper Extremity (FMA-UE) z-score (x-axis) and hippocampal volumes z-score (y-axis) for women (red) and men (blue) calculated from the FMA-UE \times Sex interactions.

Histograms for FMA-UE scores (bottom left), age (bottom middle), and lesion size (bottom right) are plotted by sex (women in red and men in blue).

remained significant when excluding participants with secondary lesions ($\beta=0.30$, $P=0.001$, $R^2=0.35$; Table S7).

Sex Effects on the Association Between Hippocampal Volume and Sensorimotor Impairment

A *t* test revealed no significant differences in FMA-UE ($t[260]=1.13$, $P=0.26$) or age ($t[249]=1.12$, $P=0.26$) between women and men. Women did have significantly larger lesions than men ($t[277]=2.9$, $P=0.004$) (Figure 3). The FMA-UE \times Sex interaction was a significant covariate for both ipsilesional ($\beta=-0.26$, $P=0.009$, $R^2=0.30$) and contralesional ($\beta=-0.27$, $P=0.006$, $R^2=0.32$) hippocampal volumes (Figure 3, Table 2), even after accounting for lesion size (ipsilesional: $\beta=-0.26$, $P=0.008$, $R^2=0.33$; contralesional: $\beta=-0.27$, $P=0.006$, $R^2=0.32$; Table 3). In the ipsilesional hippocampus, women had a positive slope ($\beta=0.26$) and men had a negative slope close to 0 ($\beta=-0.002$). In the contralesional hippocampus, women had a positive slope ($\beta=0.15$) while men had a negative slope ($\beta=-0.12$) (Figure 3). The FMA-UE \times Sex interaction remained significantly associated with both ipsilesional ($\beta=-0.31$, $P=0.008$, $R^2=0.35$) and contralesional ($\beta=-0.28$, $P=0.017$, $R^2=0.32$) hippocampal volumes, even when excluding participants with secondary lesions (Table S7).

Hippocampal Volume and Lesion Size

Larger lesion size was significantly associated with smaller ipsilesional ($\beta=-0.21$, $P<0.001$, $R^2=0.33$) but not contralesional hippocampal volume ($\beta=-0.03$, $P=0.60$, $R^2=0.30$), after adjusting for age, sex, lesioned hemisphere, and cohort (Table S12; Figure 2). Lesion size remained significantly associated with smaller ipsilesional, but not contralesional, hippocampal volume, even when excluding participants with secondary lesions ($\beta=-0.18$, $P=0.003$, $R^2=0.33$; Table S8).

Hippocampal Volume and Sensorimotor Damage

More sensorimotor damage was significantly associated with a smaller ipsilesional hippocampal volume ($\beta=-0.15$, $P=0.003$, $R^2=0.30$; Table S13). However, this association did not remain significant after including lesion size in the model ($\beta=-0.03$, $P=0.66$, $R^2=0.32$; Table S14).

DISCUSSION

In this study, associations between sensorimotor impairment, lesion size, sex, and hippocampal volume were investigated in participants with chronic stroke from 18 research cohorts in the ENIGMA Stroke Recovery Working Group.²³ Greater sensorimotor

impairment and larger lesion sizes were both significantly associated with smaller ipsilesional hippocampal volumes, and the association between sensorimotor impairment and hippocampal volume was stronger in women than in men.

To our knowledge, this is the first study to report associations between hippocampal volume and sensorimotor impairment in patients with chronic stroke. Greater sensorimotor impairment was independently associated with smaller ipsilesional hippocampal volume, even after adjusting for lesion size. This suggests that poststroke ipsilesional hippocampal integrity may be related to sensorimotor impairment. SD might explain the sensitivity of stroke-related ipsilesional hippocampal atrophy, where damaging neurotoxic signals from the core of the lesion propagate to adjacent gray matter regions.^{6–8} The blockage of blood supply during the acute phase of a stroke leads to an ionic imbalance that causes a buildup of extracellular glutamate, triggering a self-propagating wave of cell depolarization throughout neighboring gray matter.³⁸ The hippocampus is filled with tightly packed, easily excitable glutamatergic neurons and a high density of *N*-methyl-D-aspartate receptors,³⁹ making it more susceptible to damage from SD. Overexcitation of the hippocampal glutamatergic network leads to hippocampal excitotoxicity, resulting in hippocampal neuron apoptosis, which is thought to be reflected on a macroscale as reduced hippocampal volume.⁸ The damaging effects of SD are likely more prominent in the lesioned hemisphere because SD waves do not propagate easily through white matter³⁸; therefore, the waves cannot easily traverse to the contralesional hippocampus. While a magnetic resonance spectroscopy study reported evidence of hippocampal neuronal loss in the contralesional hippocampus, it was less severe and not detectable using volumetric MRI.⁸ SD still is not well understood; therefore, contralesional hippocampal damage may be caused by mild SD or might be attributed to other forms of secondary degeneration such as diaschisis.⁵ The available evidence is insufficient to support SD as the key cause of reduced ipsilesional hippocampal volumes observed in this study, and there are several other mechanisms that may explain stroke-related hippocampal damage such as chronic inflammation.⁴⁰ However, these findings could provide future directions for research investigating the mechanisms of stroke-related hippocampal damage.

One question is whether the smaller hippocampal volumes observed is reflective of general atrophy of regions across the entire ipsilesional hemisphere, or if it is specific to the hippocampus. Although the current work cannot directly address this, because Hippocampal only provides measures of hippocampal volume and total brain volume, recent work examined relationships between the volumes of 5 subcortical regions

associated with sensorimotor processing (ie, thalamus, caudate, putamen, pallidum, and nucleus accumbens) in relation to sensorimotor impairment after stroke.⁴ In chronic stroke, only the ipsilesional putamen was significantly associated with sensorimotor impairment specifically, suggesting that volumes of distinct regions are related with sensorimotor deficits. Thus, it is likely that the hippocampal association is a true relationship and not reflective of general ipsilesional atrophy.

We initially hypothesized that in addition to hippocampal damage incurred by SD, ipsilesional disruption to sensorimotor circuits may cause secondary degeneration of the ipsilesional hippocampus, possibly as a result of anatomical connectivity to damaged areas (eg, through the thalamus,¹⁵ basal ganglia,¹² sensorimotor cortex,¹⁴ or supplementary motor area¹⁶) via anterograde degeneration. While we found a significant relationship between extent of sensorimotor damage and ipsilesional hippocampal volume, this relationship became insignificant once lesion size was added into the model. This suggests that smaller hippocampal volumes are likely not attributed to secondary degeneration derived from ipsilesional disruption to sensorimotor circuits specifically. Further structural and functional connectivity research as well as longitudinal investigations may provide a more complete picture of the role of hippocampal damage in sensorimotor circuitry.

Furthermore, because the hippocampus is an important limbic system structure, it is heavily involved in learning, memory, and emotion.³⁹ Poststroke cognitive impairment, depression, and anxiety are all common pervasive symptoms in stroke survivors that interfere with rehabilitation and are associated with poor stroke outcomes.⁴¹ Limbic system disruption caused by secondary poststroke hippocampal damage may cause cognitive impairment or aggravate symptoms of depression and anxiety, which in turn, may interfere with stroke sensorimotor rehabilitation efforts. Further functional and longitudinal research is necessary to understand the relationship between hippocampal damage and sensorimotor circuits and how hippocampal volume loss may impact sensorimotor rehabilitation.

In an exploratory analysis, we found significant sex differences in the association between FMA-UE and bilateral hippocampal volume, where women showed progressively greater sensorimotor impairment with smaller hippocampal volumes compared with men. This observation suggests that women with greater sensorimotor impairment may also have more hippocampal damage or more pre-existing hippocampal atrophy compared with men. In addition, sex differences observed in the association between sensorimotor impairment and hippocampal volume did not appear to be driven by age or severity of sensorimotor impairment. Although lesion size was significantly larger in

women, the FMA-UE \times Sex interaction covariate was independently associated with hippocampal volume, even when accounting for lesion size. Overall, these findings should be considered exploratory given the unequal number of men and women in the sample. Further research is needed to confirm these findings, because our sample was unable to account for additional variables thought to influence the hippocampus in a sex-dependent way such as estrogen levels,¹⁹ dementia,¹⁷ and depression.⁴² Additionally, the current sample does not have information about race, which is known to affect stroke risk factors, possibly in a sex-dependent way.⁴³ Furthermore, the extent to which sex differences observed in stroke research are a result of physiological differences between sexes versus different contextual factors such as treatment received by women poststroke remains unclear.²¹ For example, a recent meta-analysis showed that women are less likely to receive thrombolytic treatment thought to improve stroke outcomes, compared with men.⁴⁴ Further research on sex differences in stroke is crucial to improve our understanding of the relationship between hippocampal damage and sensorimotor impairment.

Lastly, we found that larger lesion sizes were significantly associated with smaller hippocampal volumes, but only within the lesioned hemisphere, independent of sensorimotor impairment. This finding is in line with a previous study⁷ and may indicate that smaller hippocampal volumes observed in patients with stroke may be specific to the amount of stroke-related damage within the lesioned hemisphere beyond that which is attributed to age-related atrophy³⁹ or other stroke risk factors such as hypertension⁴⁵ or changes in estrogen¹⁹ that are typically observed bilaterally.

Limitations and Future Directions

This study only considered gross hippocampal volume. However, the hippocampus is composed of structurally and functionally distinct subfields, each differentially vulnerable to disease.⁴⁶ Structurally, reduced neuron density has been observed in the cells of the CA1 subfield of postmortem patients with stroke when compared with controls,⁴⁷ and larger white matter hyperintensity volume has been associated with a smaller hippocampal-amygdala transition area.⁴⁸ Functionally, while the posterior extents of the hippocampus along the long axis are thought to be more involved with memory and cognitive processing,⁴⁹ the anterior extents have been implicated in sensorimotor integration.³⁹ Further research investigating sensorimotor impairment and the hippocampus at a finer resolution, such as at the level of hippocampal subfields⁴⁹ or vertex-wise associations,⁵⁰ may reveal more specific and robust relationships that can better inform the understanding of the impact of hippocampal damage on recovery and rehabilitation.

One limitation of the Hippodeep software used in this study is that it only generates measurements for hippocampal volume and total head size and does not provide information about other brain regions such as cortical and subcortical volumes. Further research is necessary to compare the strength of associations between sensorimotor impairment and volumes of other cortical and subcortical regions in relation to associations with hippocampal volume.

In addition, although secondary lesions were discovered while manually tracing lesion masks, our findings did not change when participants with secondary lesions were excluded. Additionally, our preliminary results on lesion location only investigated sensorimotor region damage. As mentioned previously, the hippocampus is a densely connected region and further research is necessary to investigate the impact of lesion location on the association between hippocampal volume and sensorimotor impairment.

Given the focus on hippocampal volumes, another limitation of this study is the lack of cognitive and depression data. While cognitive and depressive scores are available for a small number of cohorts in the ENIGMA Stroke Recovery database, the participants with available data have very limited information. In addition, many of the participating ENIGMA Stroke Recovery research cohorts used cognitive impairment as an exclusion criterion, which is a fairly common practice in sensorimotor rehabilitation research,⁵¹ resulting in participants with no or mild cognitive deficits. However, given the high prevalence of poststroke dementia,⁵² future prospective studies collecting both sensorimotor and cognitive behavioral information across a range of impairment levels are necessary to improve our understanding of how poststroke cognitive impairment may interfere with sensorimotor rehabilitation.⁵³

Finally, the current sample is cross-sectional and cannot account for the extent of longitudinal hippocampal atrophy that may have occurred as a result of stroke, mild cognitive impairment, pre-existing dementia, or normal aging. Additionally, without longitudinal data, we cannot investigate the directionality of the association between sensorimotor impairment and hippocampal volume. Our findings reflect a cross-sectional association, which does not imply causality. Future well-powered longitudinal research should examine causal relationships between these 2 factors.

This sample also does not contain data on type or dose of rehabilitation treatment received, which could also influence sensorimotor outcomes. However, the current cross-sectional analysis serves as a first step to examining the relationship between hippocampal volumes, sensorimotor impairment, lesion volume, and sex and can be used to guide future questions using a longitudinal data set.

CONCLUSIONS

Our findings demonstrate a novel association between chronic poststroke sensorimotor impairment and hippocampal volume that may be modulated by sex. We provide supporting evidence to existing literature that reduced hippocampal volume is likely a consequence of stroke-related damage within the lesioned hemisphere. Overall, these findings provide unique insight into the role that the hippocampus may play in poststroke sensorimotor impairment.

ARTICLE INFORMATION

Received December 22, 2021; accepted March 29, 2022.

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Acknowledgments

We thank Sophia Thomopoulos for her assistance.

Sources of Funding

S.-L.L. is supported by NIH K01 HD091283; NIH R01 NS115845. A.B. and M.S.K. are supported by National Health and Medical Research Council (NHMRC) GNT1020526, GNT1045617 (A.B.), GNT1094974, and Heart Foundation Future Leader Fellowship 100784 (A.B.). P.M.T. is supported by NIH U54 EB020403. L.A.B. is supported by the Canadian Institutes of Health Research (CIHR). C.M.B. is supported by NIH R21 HD067906. W.D.B. is supported by the Health Research Council of New Zealand. J.M.C. is supported by NIH R01HD091375. A.B.C. is supported by NIH R01NS076348-01, Hospital Israelita Albert Einstein 2250-14, CNPq/305568/2016-7. A.N.D. is supported by funding provided by the Texas Legislature to the Lone Star Stroke Clinical Trial Network. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Government of the United States or the State of Texas. N.E.-B. is supported by Australian Research Council NIH DE180100893. W.F. is supported by NIH P20 GM109040. F.G. is supported by Wellcome Trust (093957). B.H. is funded by and NHMRC fellowship (1125054). S.A.K. is supported by NIH P20 HD109040. F.B. is supported by Italian Ministry of Health, RC 20, 21. N.S. is supported by NIH R21NS120274. N.J.S. is supported by NIH/National Institute of General Medical Sciences (NIGMS) 2P20GM109040-06, U54-GM104941. S.R.S. is supported by European Research Council (ERC) (NGBMI, 759370). G.S. is supported by Italian Ministry of Health RC 18-19-20-21A. M.T. is supported by National Institute of Neurological Disorders and Stroke (NINDS) R01 NS110696. G.T.T. is supported by Temple University sub-award of NIH R24 -NHLBI (Dr Mickey Selzer) Center for Experimental Neurorehabilitation Training. N.J.S. is funded by NIH/National Institute of Child Health and Human Development (NICHD) 1R01HD094731-01A1.

Disclosures

Amy Brodtmann is on the editorial boards of *Neurology* and *International Journal of Stroke* and sits on a Biogen Australia Scientific Advisory Committee. Steven C. Cramer serves as a consultant for Abbvie, Constant Therapeutics, MicroTransponder, Neuroolutions, SanBio, Panaxium, NeuExcell, Elevian, Medtronic, and TRCare. Brenton Hordacre has a clinical partnership with Fourier Intelligence. The remaining authors have no disclosures to report.

Supplemental Material

Data S1
Tables S1–S14
Figure S1

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Supplemental Material

Data S1.

Data demographics following removal of multivariate outliers and segmentations that failed quality control

3 participants were identified as multivariate outliers using the Mahalanobis distance. These participants were excluded from the analysis. Additionally, 18 participants were excluded from the ipsilesional analysis (**Table S1**) and 5 participants were excluded from the contralesional analysis (**Table S2**), due to hippocampal segmentations that failed quality control. More details regarding ENIGMA quality control protocols can be found in Zavaliangos-Petropulu et al., 2020 and Liew et al., 2020. Briefly, a segmentation failed quality control if the segmentation grossly underestimated the hippocampus, overestimated the hippocampus by including regions of the brain outside of the hippocampus, or missed the hippocampus entirely. To ensure that differing sample sizes for the ipsilesional and contralesional analyses did not influence the results, we performed a supplemental analysis only including participants with hippocampal segmentations that passed quality control for both ipsilesional and contralesional hippocampi (**Tables S3-S6**).

Table S1. Detailed demographics for the sample used to analyze sensorimotor impairment and ipsilesional hippocampal volume.

Cohort	Women				Men			
	N	Age (yrs)	FMA-UE	Lesion Size (cc)	N	Age (yrs)	FMA-UE	Lesion Size (cc)
Cohort 1	10	53 (14,31-75)	35 (16,0-58)	8.1 (31.5,1.1-96.6)	26	65 (12,42-80)	44 (13,19-56)	3.8 (7.6,0-37)
Cohort 2	3	64 (17,51-85)	31 (17,14-48)	9.8 (24.6,6.3-55.5)	5	71 (18,39-74)	37 (22,13-46)	10 (23.4,4.2-34.1)
Cohort 3	6	62 (9,35-85)	15 (7,5-18)	21.6 (16.1,1.3-112.4)	6	52 (15,33-71)	29 (11,5-40)	7.6 (6.7,0.6-113.4)
Cohort 4	5	34 (19,30-68)	11 (5,9-34)	48.8 (23.4,9.7-90)	10	46 (11,32-63)	9 (11,1-24)	31.9 (30.8,1-130.2)
Cohort 5	12	62.5 (14,44-81)	55 (21,22-65)	1.7 (6.2,0.1-70.2)	16	67 (18,50-81)	40 (32,8-65)	5.2 (66.6,0.3-237.7)
Cohort 6	3	63 (10, 2-72)	65 (0,65-65)	5 (4.3,0.5-9.1)	7	59 (14,49-66)	64 (9,45-65)	1.3 (0.5,0.6-2.2)
Cohort 7	5	61 (4,57-65)	49 (43,14-63)	4.3 (1.3,0.3-6.9)	9	53 (10,45-69)	63 (4,6-65)	1.5 (1.2,0.04-5.3)
Cohort 8	4	58 (16,45-74)	50 (10,32-55)	45.2 (43,0.7-64.6)	7	56 (9,45-68)	45 (15,25-55)	35.8 (47.2,0.9-103.9)
Cohort 9	3	59 (1, 8-60)	42 (11,26-49)	2.5 (11.6,0.8-24)	8	59 (5,45-68)	36 (20,15-49)	4.9 (22,0.7-53.7)
Cohort 10	4	61 (11,46-73)	55 (9,35-58)	10.9 (28,0.4-59)	3	58 (4,56-64)	43 (11,37-59)	37 (27.3,1.4-55.9)
Cohort 11	6	65 (5,51-75)	47 (24,23-61)	5.2 (31.3,0.4-201.4)	16	59 (10,23-75)	49 (18,29-64)	5.8 (42,0.6-71)
Cohort 12	4	51 (16,32-62)	58 (8,54-63)	1.8 (14.5,0.3-55.9)	9	58 (7,47-80)	48 (11,38-62)	8.2 (17.8,1.3-98)
Cohort 13	4	68 (20,31-75)	60 (4,51-62)	23.2 (55,0.5-107.5)	7	68 (19,52-83)	37 (31,19-61)	4.5 (30.3,0.2-62.6)
Cohort 14	17	50 (15,36-79)	41 (15,24-47)	13.6 (44.7,0.7-143.6)	11	50 (15,25-76)	44 (9,31-53)	3.8 (12.5,0.1-32.4)
Cohort 15	3	47 (11,42-63)	18 (5,11-21)	36.7 (91.4,3.2-186.1)	7	62 (12,51-76)	35 (16,23-60)	8.6 (3.3,3-97.5)
Cohort 16	14	68 (12,43-93)	48 (33,20-65)	12.1 (24.9,1.1-54.4)	26	65 (9,45-81)	47 (26,4-62)	8 (25.2,0.5-111.8)
Cohort 17	15	68 (19,37-79)	38 (34,8-64)	7.6 (31.2,0.5-188.4)	20	72 (12,51-80)	56 (11,23-65)	5.2 (22,0.3-110.8)
Cohort 18	12	62 (15,34-85)	28 (5,14-34)	15.6 (47.9,0.8-136.9)	13	65 (17,50-78)	27 (4,23-33)	3.1 (3.6,0.7-34.1)
Total	130	60 (20,30-93)	39 (29,0-65)	9.3 (39.5,0.11-201.4)	206	62 (16,23-83)	44 (25,1-65)	5.6 (24.1,0.04-237.7)

Demographics for women and men are broken down by cohort. Sample size (N) and median (IQR, range) of age, FMA-UE, and raw lesion size are reported.

Table S2. Detailed demographics for the sample used to analyze sensorimotor impairment and contralesional hippocampal volume.

Cohort	Women				Men			
	N	Age (yrs)	FMA-UE	Lesion Size (cc)	N	Age (yrs)	FMA-UE	Lesion Size (cc)
Cohort 1	10	53 (14,31-75)	35 (16,0-58)	8.1 (31.5,1.1-96.6)	28	64 (17,32-80)	44 (13,19-56)	4.9 (12,0.04-120.8)
Cohort 2	6	66 (9,51-85)	23 (29,13-48)	38 (39,6.3-137.4)	6	71 (14,39-74)	36 (17,13-46)	19 (26.2,4.2-34.1)
Cohort 3	6	62 (9,35-85)	15 (7,5-18)	21.6 (16.1,1.3-112.4)	8	57 (17,33-71)	22 (22,5-40)	10.5 (50.6,0.6-171.2)
Cohort 4	5	34 (19,30-68)	11 (5,9-34)	48.8 (23.4,9.7-90)	12	45 (11,32-63)	8 (11,1-24)	31.9 (38.8,4.5-130.2)
Cohort 5	12	63 (14,44-81)	55 (21,22-65)	1.7 (6.2,0.1-70.2)	16	67 (18,50-81)	40 (32,8-65)	5.2 (66.6,0.3-237.7)
Cohort 6	3	63 (10,52-72)	65 (0,65-65)	5 (4.3,0.5-9.1)	7	59 (14,49-66)	64 (9,45-65)	1.3 (0.5,0.6-2.2)
Cohort 7	5	61 (4,57-65)	49 (43,14-63)	4.3 (1.3,0.3-6.9)	9	53 (10,45-69)	63 (4,6-65)	1.5 (1.2,0.04-5.3)
Cohort 8	4	58 (16,45-74)	50 (10,32-55)	45.2 (43,0.7-64.6)	7	56 (9,45-68)	45 (15,25-55)	35.8 (47.2,0.9-103.9)
Cohort 9	3	59 (1,58-60)	42 (11,26-49)	2.5 (11.6,0.8-24)	8	59 (5,45-68)	36 (20,15-49)	4.9 (22,0.7-53.7)
Cohort 10	4	61 (11,46-73)	55 (9,35-58)	10.9 (28,0.4-59)	4	57 (4,53-64)	43 (5,37-59)	39.2 (16.9,1.4-55.9)
Cohort 11	6	65 (5,51-75)	47 (24,23-61)	5.2 (31.3,0.4-201.4)	16	59 (10,23-75)	49 (18,29-64)	5.8 (42,0.6-71)
Cohort 12	4	51 (16,32-62)	58 (8,54-63)	1.8 (14.5,0.3-55.9)	8	58 (9,47-80)	51 (11,43-62)	6.5 (9,1.3-34.3)
Cohort 13	4	68 (20,31-75)	60 (4,51-62)	23.2 (55,0.5-107.5)	8	66 (16,52-83)	40 (27,19-61)	3.4 (27,0.2-62.6)
Cohort 14	18	49 (14,36-79)	41 (15,24-47)	14.3 (45.9,0.7-143.6)	10	54 (15,25-76)	43 (9,31-53)	3.1 (10.8,0.1-16.5)
Cohort 15	3	47 (11,42-63)	18 (5,11-21)	36.7 (91.4,3.2-186.1)	7	62 (12,51-76)	35 (16,23-60)	8.6 (3.3,3-97.5)
Cohort 16	14	68 (12,43-93)	48 (33,20-65)	12.1 (24.9,1.1-54.4)	26	65 (9,45-81)	47 (26,4-62)	8 (25.2,0.5-111.8)
Cohort 17	15	68 (19,37-79)	38 (34,8-64)	7.6 (31.2,0.5-188.4)	20	72 (12,51-80)	56 (11,23-65)	5.2 (22,0.3-110.8)
Cohort 18	12	62 (15,34-85)	28 (5,14-34)	15.6 (47.9,0.8-136.9)	15	64 (14,50-78)	27 (4,19-34)	4.8 (18.8,0.7-100.4)
Total	134	61 (20,30-93)	39 (29,0-65)	9.7(42.1,0.1-201.4)	215	62 (16,23-83)	43 (26,1-65)	5.8 (26.9,0.04-237.7)

Demographics for women, men, and total are broken down by cohort. Sample size (N) and median (IQR, range) of age, FMA-UE, and raw lesion size are reported.

Table S3. Summary statistics from robust mixed-effects linear regression to test associations between ipsilesional hippocampal volume and sensorimotor impairment (*top*) and contralesional hippocampal volume and sensorimotor impairment (*bottom*) in participants who passed quality control for bilateral hippocampi.

<i>Hippocampus ~ FMA-UE + Sex + Lesioned Hemisphere + Age + random(Cohort)</i>			
<i>Covariates</i>	<i>Beta(CI)</i>	<i>SE</i>	<i>p-value</i>
<i>IPSILESIONAL HIPPOCAMPAL VOLUME (N=334; R²=0.27)</i>			
FMA-UE	0.16 (0.05 – 0.27)	0.06	0.004
Sex	-0.54 (-0.74 – -0.34)	0.10	<0.001
Lesioned Hemisphere	0.19 (-0.01 – 0.39)	0.10	0.06
Age	-0.32 (-0.43 – -0.22)	0.05	<0.001
<i>CONTRALESIONAL HIPPOCAMPAL VOLUME (N=334; R²=0.33)</i>			
FMA-UE	0.02 (-0.09 – 0.12)	0.05	0.78
Sex	-0.55 (-0.75 – -0.36)	0.10	<0.001
Lesioned Hemisphere	-0.36 (-0.56 – -0.16)	0.10	0.001
Age	-0.41 (-0.51 – -0.32)	0.05	<0.001

The full model as well as the sample size (*N*), conditional *R*², beta coefficient (*Beta*) with 95% confidence interval (*CI*), standard error (*SE*), and uncorrected *p-value* for all fixed effect covariates are reported.

Significant covariates are denoted in bold.

Table S4. Summary statistics from robust mixed-effects linear regression to test associations between ipsilesional hippocampal volume and sensorimotor impairment (*top*) and contralesional hippocampal volume and sensorimotor impairment (*bottom*) when including a sensorimotor impairment and sex interaction in participants who passed quality control for bilateral hippocampi.

<i>Hippocampus ~ FMA-UE*Sex + FMA-UE + Sex + Lesioned Hemisphere + Age + random(Cohort)</i>			
<i>Covariates</i>	<i>Beta(CI)</i>	<i>SE</i>	<i>p-value</i>
<i>IPSILESIONAL HIPPOCAMPAL VOLUME (N=334; R²=0.29)</i>			
FMA-UE	0.32 (0.16 – 0.47)	0.08	<0.001
FMA-UE*Sex	-0.27 (-0.47 – -0.07)	0.10	0.007
Sex	-0.54 (-0.74 – -0.35)	0.10	<0.001
Lesioned Hemisphere	0.18 (-0.03 – 0.38)	0.10	0.09
Age	-0.32 (-0.43 – -0.22)	0.05	<0.001
<i>CONTRALESIONAL HIPPOCAMPAL VOLUME (N=334; R²=0.35)</i>			
FMA-UE	0.17 (0.02 – 0.32)	0.08	0.028
FMA-UE*Sex	-0.27 (-0.46 – -0.08)	0.10	0.006
Sex	-0.56 (-0.76 – -0.37)	0.10	<0.001
Lesioned Hemisphere	-0.38 (-0.58 – -0.19)	0.10	<0.001
Age	-0.42 (-0.51 – -0.32)	0.05	<0.001

The full model as well as the sample size (*N*), conditional *R*², beta coefficient (*Beta*) with 95% confidence interval (*CI*), and uncorrected *p-value* for all fixed effect covariates are reported. Significant covariates are denoted in bold.

Table S5. Summary statistics from robust mixed-effects linear regression to test associations between ipsilesional hippocampal volume and sensorimotor impairment (*top*) and contralesional hippocampal volume and sensorimotor impairment (*bottom*) when including lesion size as a covariate in participants who passed quality control for bilateral hippocampi.

<i>Hippocampus ~ Lesion Size + FMA-UE*Sex + FMA-UE + Sex + Lesioned Hemisphere + Age + random(Cohort)</i>			
<i>Covariates</i>	<i>Beta(CI)</i>	<i>SE</i>	<i>p-value</i>
<i>IPSILESIONAL HIPPOCAMPAL VOLUME (N=334; R²=0.32)</i>			
FMA-UE	0.27 (0.11 – 0.42)	0.08	0.001
FMA-UE*Sex	-0.27 (-0.46 – -0.08)	0.10	0.006
Lesion Size	-0.19 (-0.30 – -0.09)	0.05	<0.001
Sex	-0.60 (-0.79 – -0.40)	0.10	<0.001
Lesioned Hemisphere	0.17 (-0.03 – 0.37)	0.10	0.09
Age	-0.36 (-0.46 – -0.26)	0.05	<0.001
<i>CONTRALESIONAL HIPPOCAMPAL VOLUME (N=334; R²=0.34)</i>			
FMA-UE	0.17 (0.01 – 0.32)	0.08	0.032
FMA-UE*Sex	-0.27 (-0.46 – -0.08)	0.10	0.006
Lesion Size	-0.01 (-0.11 – 0.09)	0.05	0.84
Sex	-0.57 (-0.76 - -0.37)	0.10	<0.001
Lesioned Hemisphere	-0.38 (-0.52 – -0.32)	0.10	<0.001
Age	-0.42 (-0.52 – -0.32)	0.05	<0.001

The full model as well as the sample size (*N*), conditional *R*², beta coefficient (*Beta*) with 95% confidence interval (*CI*), standard error (*SE*), and uncorrected *p-value* for all fixed effect covariates are reported. Significant covariates are denoted in bold.

Table S6. Summary statistics from robust mixed-effects linear regression to test associations between ipsilesional hippocampal volume and lesion size (*top*) and contralesional hippocampal volume and lesion size (*bottom*) in participants who passed quality control for bilateral hippocampi.

<i>Hippocampus ~ Lesion Size + Sex + Lesioned Hemisphere + Age + random(Cohort)</i>			
<i>Covariates</i>	<i>Beta(CI)</i>	<i>SE</i>	<i>p-value</i>
<i>IPSILESIONAL HIPPOCAMPAL VOLUME (N=334; R²=0.32)</i>			
Lesion Size	-0.22 (-0.32 – -0.12)	0.05	<0.001
Sex	-0.59 (-0.79 – -0.39)	0.10	<0.001
Lesioned Hemisphere	0.17 (-0.03 – 0.36)	0.10	0.10
Age	-0.35 (-0.45 – -0.25)	0.05	<0.001
<i>CONTRALESIONAL HIPPOCAMPAL VOLUME (N=334; R²=0.33)</i>			
Lesion Size	-0.01 (-0.11 – 0.09)	0.05	0.81
Sex	-0.56 (-0.75 – -0.36)	0.10	<0.001
Lesioned Hemisphere	-0.36 (-0.56 – -0.17)	0.10	0.001
Age	-0.42 (-0.52 – -0.32)	0.05	<0.001

The full model as well as the sample size (*N*), conditional *R*², beta coefficient (*Beta*) with 95% confidence interval (*CI*), standard error (*SE*), and uncorrected *p-value* for all fixed effect covariates are reported. Significant covariates are denoted in bold.

Table S7. Summary statistics from robust mixed-effects linear regression to test associations between ipsilesional hippocampal volume and sensorimotor impairment (*top*) and contralesional hippocampal volume and sensorimotor impairment (*bottom*) when including lesion size as a covariate and excluding participants with secondary lesions.

<i>Hippocampus ~ Lesion Size + FMA-UE*Sex + Lesioned Hemisphere + Age + random(Cohort)</i>			
<i>Covariates</i>	<i>Beta(CI)</i>	<i>SE</i>	<i>p-value</i>
IPSILESIONAL HIPPOCAMPAL VOLUME (N=240; R²=0.35)			
FMA-UE	0.30 (0.12 – 0.48)	0.09	0.001
FMA-UE*Sex	-0.31 (-0.53 – -0.08)	0.11	0.008
Lesion Size	-0.14 (-0.27 – -0.02)	0.06	0.019
Sex	-0.57 (-0.80 – -0.35)	0.11	<0.001
Lesioned Hemisphere	0.18 (-0.06 – 0.41)	0.12	0.14
Age	-0.29 (-0.41 – -0.18)	0.06	<0.001
CONTRALESIONAL HIPPOCAMPAL VOLUME (N=245 R²=0.32)			
FMA-UE	0.18 (0.00 – 0.35)	0.09	0.05
FMA-UE*Sex	-0.28 (-0.50 – -0.05)	0.12	0.017
Lesion Size	0.05 (-0.08 – 0.17)	0.06	0.45
Sex	-0.45 (-0.68 – -0.22)	0.12	<0.001
Lesioned Hemisphere	-0.38 (-0.62 – -0.15)	0.12	0.001
Age	-0.36 (-0.48 – -0.25)	0.06	<0.001

The full model as well as the sample size (*N*), conditional *R*², beta coefficient (*Beta*) with 95% confidence interval (*CI*), standard error (*SE*), and uncorrected *p-value* for all fixed effect covariates are reported. Significant covariates are denoted in bold.

Table S8. Summary statistics from robust mixed-effects linear regression to test associations between ipsilesional hippocampal volume and lesion size (*top*) and contralesional hippocampal volume and lesion size (*bottom*) after excluding participants with secondary lesions.

<i>Hippocampus ~ Lesion Size + Sex + Lesioned Hemisphere + Age + random(Cohort)</i>			
<i>Covariates</i>	<i>Beta(CI)</i>	<i>SE</i>	<i>p-value</i>
<i>IPSILESIONAL HIPPOCAMPAL VOLUME (N=240; R²=0.33)</i>			
Lesion Size	-0.18 (-0.30 – -0.06)	0.06	0.003
Sex	-0.58 (-0.80 – -0.35)	0.12	<0.001
Lesioned Hemisphere	0.16 (-0.08 – 0.39)	0.12	0.19
Age	-0.28 (-0.40 – -0.16)	0.06	<0.001
<i>CONTRALESIONAL HIPPOCAMPAL VOLUME (N=245; R²=0.29)</i>			
Lesion Size	0.04 (-0.08 – 0.16)	0.06	0.53
Sex	-0.45 (-0.68 – -0.22)	0.12	<0.001
Lesioned Hemisphere	-0.37 (-0.60 – -0.14)	0.12	0.002
Age	-0.36 (-0.48 – -0.24)	0.06	<0.001

The full model as well as the sample size (*N*), conditional R^2 , beta coefficient (*Beta*) with 95% confidence interval (*CI*), standard error (*SE*), and uncorrected *p-value* for all fixed effect covariates are reported.

Significant covariates are denoted in bold.

Table S9. To ensure no redundancy in the included independent variables, collinearity for variables in every model tested was ruled out (variance inflation factor ≤ 2.5).

Model 1		Model 2		Model 3	
Covariates	VIF	Covariates	VIF	Covariates	VIF
FMA-UE	1.0	FMA-UE	2.1	Lesion Size	1.1
Sex	1.0	Sex	1.0	FMA-UE	2.1
Age	1.0	FMA-UE*Sex	2.1	Sex	1.0
Lesioned Hemisphere	1.0	Age	1.0	FMA-UE*Sex	2.1
		Lesioned Hemisphere	1.0	Age	1.1
				Lesioned Hemisphere	1.0
Model 4		Model 5		Model 6	
Covariates	VIF	Covariates	VIF	Covariates	VIF
Lesion Size	1.1	Sensorimotor Damage	1.1	Lesion Size	1.7
Sex	1.0	Sex	1.0	Sensorimotor Damage	1.7
Age	1.0	Age	1.1	Sex	1.0
Lesioned Hemisphere	1.0	Lesioned Hemisphere	1.0	Age	1.1
				Lesioned Hemisphere	1.0

Variance inflation factors (VIF) for each variable in every model testing associations with ipsilesional hippocampal volume is listed.

Table S10. To ensure no redundancy in the included independent variables, variance inflation factors (VIF) for each variable in every model testing associations with contralesional hippocampal volume is listed.

Model 1		Model 2		Model 3	
Covariates	VIF	Covariates	VIF	Covariates	VIF
FMA-UE	1.0	FMA-UE	2.2	Lesion Size	1.0
Sex	1.0	Sex	1.0	FMA-UE	2.3
Age	1.0	FMA-UE*Sex	2.2	Sex	1.0
Lesioned Hemisphere	1.0	Age	1.0	FMA-UE*Sex	2.2
		Lesioned Hemisphere	1.0	Age	1.1
				Lesioned Hemisphere	1.0
Model 4					
Covariates	VIF				
Lesion Size	1.0				
Sex	1.0				
Age	1.0				
Lesioned Hemisphere	1.0				

Table S11. Summary statistics from robust mixed-effects linear regression to test associations between ipsilesional hippocampal volume and sensorimotor impairment (*top*) and contralesional hippocampal volume and sensorimotor impairment (*bottom*).

<i>Hippocampal Volume ~ FMA-UE + Sex + Lesioned Hemisphere + Age + random(Cohort)</i>			
<i>Covariates</i>	<i>Beta(CI)</i>	<i>SE</i>	<i>p-value</i>
<i>IPSILESIONAL HIPPOCAMPAL VOLUME (N=336; R²=0.27)</i>			
FMA-UE	0.16 (0.05 – 0.27)	0.06	0.005
Sex	-0.53 (-0.73 – -0.33)	0.10	<0.001
Lesioned Hemisphere	0.19 (-0.01 – 0.39)	0.10	0.06
Age	-0.32 (-0.42 – -0.22)	0.05	<0.001
<i>CONTRALESIONAL HIPPOCAMPAL VOLUME (N=349; R²=0.29)</i>			
FMA-UE	0.003 (-0.10 – 0.11)	0.05	0.96
Sex	-0.50 (-0.69 – -0.31)	0.10	<0.001
Lesioned Hemisphere	-0.32 (-0.51 – -0.13)	0.10	0.001
Age	-0.41 (-0.51 – -0.32)	0.05	<0.001

The full model as well as the sample size (*N*), conditional R^2 , beta coefficient (*Beta*) with 95% confidence interval (*CI*), standard error (*SE*), and uncorrected *p-value* for all fixed effect covariates are reported. Significant covariates are denoted in bold.

Table S12. Summary statistics from robust mixed-effects linear regression to test associations between ipsilesional hippocampal volume and lesion size (*top*) and contralesional hippocampal volume and lesion size (*bottom*).

<i>Hippocampal Volume ~ Lesion Size + Sex + Lesioned Hemisphere + Age + random(Cohort)</i>			
<i>Covariates</i>	<i>Beta(CI)</i>	<i>SE</i>	<i>p-value</i>
<i>IPSILESIONAL HIPPOCAMPAL VOLUME (N=336; R²=0.33)</i>			
Lesion Size	-0.21 (-0.31 – -0.12)	0.05	<0.001
Sex	-0.58 (-0.77 – -0.38)	0.10	<0.001
Lesioned Hemisphere	0.16 (-0.03 – 0.36)	0.10	0.10
Age	-0.35 (-0.45 – -0.25)	0.05	<0.001
<i>CONTRALESIONAL HIPPOCAMPAL VOLUME (N=349; R²=0.30)</i>			
Lesion Size	-0.03 (-0.12 – 0.07)	0.05	0.60
Sex	-0.51 (-0.70 – -0.32)	0.10	<0.001
Lesioned Hemisphere	-0.32 (-0.51 – -0.13)	0.10	0.001
Age	-0.42 (-0.52 – -0.32)	0.05	<0.001

The full model as well as the sample size (*N*), conditional R², beta coefficient (*Beta*) with 95% confidence interval (*CI*), standard error (*SE*), and uncorrected *p-value* for all fixed effect covariates are reported.

Significant covariates are denoted in bold.

Table S13. Summary statistics from robust mixed-effects linear regression to test associations between ipsilesional hippocampal volume and sensorimotor damage.

<i>Hippocampal Volume ~ Sensorimotor Damage + Sex + Lesioned Hemisphere + Age + random(Cohort)</i>			
<i>Covariates</i>	<i>Beta(CI)</i>	<i>SE</i>	<i>p-value</i>
<i>IPSILESIONAL HIPPOCAMPAL VOLUME (N=334; R²=0.30)</i>			
Sensorimotor Damage	-0.15 (-0.25 – -0.05)	0.05	0.003
Sex	-0.56 (-0.76 – -0.36)	0.10	<0.001
Lesioned Hemisphere	0.17 (-0.03 – 0.37)	0.10	0.10
Age	-0.34 (-0.45 – -0.24)	0.05	<0.001

Two participants were removed from the analysis due to poor image registration. The full model as well as the sample size (*N*), conditional R^2 , beta coefficient (*Beta*) with 95% confidence interval (*CI*), standard error (*SE*), and uncorrected *p-value* for all fixed effect covariates are reported. Significant covariates are denoted in bold.

Table S14. Summary statistics from robust mixed-effects linear regression to test associations between ipsilesional hippocampal volume and sensorimotor damage after accounting for lesion size.

<i>Hippocampal Volume ~ Sensorimotor Damage + Lesion Size + Sex + Lesioned Hemisphere + Age + random(Cohort)</i>			
<i>Covariates</i>	<i>Beta(CI)</i>	<i>SE</i>	<i>p-value</i>
<i>IPSILESIONAL HIPPOCAMPAL VOLUME (N=334; R²=0.30)</i>			
Sensorimotor Damage	-0.03 (-0.15 – -0.10)	0.06	0.66
Lesion Size	-0.20 (-0.32 – -0.38)	0.06	0.002
Sex	-0.58 (-0.78 – -0.38)	0.10	<0.001
Lesioned Hemisphere	0.16 (-0.03 – 0.36)	0.10	0.10
Age	-0.35 (-0.46 – -0.25)	0.05	<0.001

Two participants were removed from the analysis due to poor image registration. The full model as well as the sample size (*N*), conditional R², beta coefficient (*Beta*) with 95% confidence interval (*CI*), standard error (*SE*), and uncorrected *p-value* for all fixed effect covariates are reported. Significant covariates are denoted in bold.

Figure S1. Lesion density maps for lesions from participants with cohort-reported left and right hemisphere lesions, and without any secondary lesions (e.g., bilateral, brainstem or cerebellar lesions), overlaid on the Montreal Neurological Institute (MNI) MNI-152 template.

