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Hippocampal Asymmetry Increases with Age

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Abstract: It is unclear whether differences between the two brain hemispheres become larger or smaller with increasing age. Given that the hippocampus is particularly susceptible to age-related changes, here, we set out to investigate the correlation between chronological age and hippocampal asymmetry, both for the hippocampal complex as a whole and in cytoarchitectonically defined subregions (cornu ammonis 1, 2, 3, dentate gyrus, subiculum, and entorhinal cortex). We analyzed T1-weighted data of the brain from a sample of 725 healthy individuals (406 women/319 men) spanning a wide age range (36–100 years) from The Lifespan Human Connectome Project in Aging. Correlations between the absolute asymmetry index and chronological age were positive for all six subregions and also for the hippocampal complex as a whole, albeit effects the effects were not significant for the dentate gyrus. This suggests that, overall, hippocampal asymmetry increases with increasing age (i.e., the left and right hippocampi become more different over time). Given that the subregions of the hippocampal complex serve different brain functions, follow-up research is needed to explore the functional implications within the framework of brain aging. In addition, longitudinal studies will be necessary to confirm the observed cross-sectional effects.

Keywords: age; asymmetry; brain; cytoarchitecture; hippocampus; MRI

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1. Introduction

It is well established that some brain functions are predominantly processed in one or the other hemisphere and that corresponding brain regions located in the left and right hemisphere differ from each other structurally and functionally [1–6]. Several reports and theories posit that structural asymmetry as well as functional lateralization change with increasing age [7–17]. Some of these theories further specify that such changes help to retain cognitive functioning and mitigate age-related brain atrophy [7,8,13,15]. However, despite the significance of age-related changes in structural asymmetry and functional lateralization, our current knowledge about the magnitude of change as well as the direction of change (decrease vs. increase) is inconclusive at best.

The hippocampal complex is heavily implicated in ageing processes [18–22] and its subregions differ in their age-related volume loss [19–23]. In addition, there is some evidence of asymmetric atrophy later in life [24], but see also [18]. Thus, here, we set out to investigate hippocampal asymmetry as well as changes in hippocampal asymmetry over time, both for the hippocampal complex as a whole and in cytoarchitectonically defined subregions (cornu ammonis (CA) 1, 2 and 3, dentate gyrus, subiculum, and entorhinal cortex). More specifically, in terms of changes in hippocampal asymmetry over time, we investigated the correlation between chronological age and the absolute asymmetry of the hippocampal complex (its subregions, respectively). Working with absolute asymmetry allows for the possibility that asymmetry itself, as well as age-related asymmetry changes, differ across brains. For example, if there was an increase in asymmetry over time to opposite sites (e.g., more leftward in some brains and more rightward in others), these

effects could cancel each other out because directional asymmetry is expressed by negative and positive values (leftward/rightward). In contrast, absolute asymmetry (no direction) is always positive and solely captures the magnitude of the asymmetry or change in magnitude, respectively. Thus, the absolute asymmetry index was the focus of interest for the main analysis. However, supplemental analyses using directional asymmetry were conducted to establish if hippocampal (sub)regions showed a leftward or rightward asymmetry independent of aging; to determine whether there was a change in the direction of asymmetry with increasing age, as well as to compare the outcomes when using the absolute and directional asymmetry index.

2. Materials and Methods

The image data and participant information were obtained from the Lifespan Human Connectome Project in Aging [25] via the National Institute of Mental Health Data Archive (NDA—https://nda.nih.gov). Specifically, we obtained the data from Lifespan 2.0, which contains T1-weighted images as well as the epidemiological information for a sample of 725 healthy participants (406 women/319 men) spanning a wide age range (36–100 years) collected at four acquisition sites (Washington University St. Louis, University of Minnesota, Massachusetts General Hospital, and University of California, Los Angeles). Descriptive statistics are provided in Table 1. All participants gave their informed consent, and the study was approved by the local IRBs. Additional local ethics approval for the data analysis was obtained from the University of Auckland (UoA) ethics committee (Protocol No. 022375).

Table 1. Descriptive statistics.

Variable	Statistics
N	725
Sex (F/M)	406/319
Age (Mean ± SD [range])	60.36 ± 15.73 [36–100]
Handedness (L/R)	76/649
Handedness Score (Mean ± SD (range))	66.92 ± 48.76 [−100–100]
TIV (Mean ± SD (range))	1.453 ± 152 [1.021–1.959] liters
N by Site (MGH, UCLA, UMinn, WashU)	163, 148, 205, 209

F = females; M = males, SD = standard deviation; TIV = total intracranial volume; MGH = Massachusetts General Hospital; UCLA = University of California, Los Angeles; UMinn = University of Minnesota; WashU = Washington University St. Louis

All brain images were processed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm) and the CAT12 toolbox (http://dbm.neuro.uni-jena.de/cat), as previously described [19,26–29]. In short, images were first de-noised, bias-corrected, and subsequently segmented into gray matter, white matter, and cerebrospinal fluid using a partial volume estimation algorithm. The gray matter segments were corrected for misclassifications due to white matter hyperintensities and then spatially normalized to the Shooting template in MNI152NLin2009c space (as provided with the CAT12 toolbox) using 12-parameter affine transformations and high-dimensional warping [30]. Finally, to preserve the original gray matter volume, the normalized gray matter segments were modulated using the Jacobian determinants derived from the normalization matrix [31–33]. In addition, the total intracranial volume (TIV) was calculated automatically during CAT12's tissue segmentation step to be later included as a co-variate in the statistical model.

To extract the hippocampal (sub)volumes, we first multiplied the processed gray matter segments with the subarea-specific probability maps [34] provided by the Julich brain atlas v2.9 [35], as described in detail elsewhere [19,26–29]. This voxel-wise integration yielded a probability-weighted measure of gray matter content within each left and right CA1, CA2, CA3, dentate gyrus, subiculum, and entorhinal cortex (in mm^3). The gray matter content for the hippocampal complex as a whole (hippo) was calculated by adding the volumes of all aforementioned subareas (hippo = CA1 + CA2 + CA3 + dentate gyrus + subiculum + entorhinal cortex). Then, we calculated the asymmetry index by

applying the following formula to the left and right hippocampal (sub)volumes [36,37]: (right − left)/(0.5 × (right + left)). This resulted in positive values (rightward asymmetry) and negative values (leftward asymmetry). Finally, we calculated the absolute asymmetry index for all hippocampal (sub)volumes (non-directional asymmetry).

All subsequent statistical analyses were conducted in Matlab (The MathWorks, Natick, MA, USA), and mixed models were applied to assess the Pearson correlations between age and hippocampal asymmetries. The absolute asymmetry indices for all six subregions as well as the hippocampal complex as a whole were used as dependent variables; age as the independent variable; sex, handedness, and TIV as variables of no interest; and site as a random variable. Significance levels were set at $p \leq 0.05$ after applying corrections for multiple comparisons by controlling the false discovery rate [38,39]. In addition to this main analysis using the absolute asymmetry index, we conducted a supplemental analysis repeating the aforementioned model but using the directional asymmetry index. This enabled us to calculate the asymmetry direction at the mean age of the sample, to test for a possible change in asymmetry direction with increasing age, as well as to compare the outcomes when using the absolute and directional asymmetry index.

3. Results

As shown in Table 2, at the sample mean age of 60.36 years, significant rightward asymmetries were observed for CA1, CA2, CA3, subiculum and also for the hippocampal complex as a whole. In contrast, significant leftward asymmetries were detected for the dentate gyrus and the entorhinal cortex. On average, there was no change in asymmetry direction over time for any (sub)region (i.e., leftward remained leftward, rightward remained rightward).

Table 2. Hippocampal asymmetries (directional) at the sample mean age (60.36 years).

Region	Change in Asymmetry	Cohen's d	T | df	*p*, Corrected
CA1	rightward	1.14	30.5 | 720	<0.001
CA2	rightward	1.39	37.4 | 720	<0.001
CA3	rightward	0.30	7.9 | 720	<0.001
DG	leftward	−0.22	−5.9 | 720	<0.001
Subiculum	rightward	1.45	38.9 | 720	<0.001
Entorhinal	leftward	−0.17	−4.4 | 720	<0.001
Hippo	rightward	0.68	18.2 | 720	<0.001

CA1, 2, 3 = cornu ammonis 1, 2, 3; DG = dentate gyrus; df = degrees of freedom.

As shown in Table 3 and Figure 1, correlations between the absolute asymmetry index and chronological age were positive for all subregions and also for the hippocampal complex as a whole (i.e., the older the brain, the larger the differences between the two hemispheres), albeit effects were not significant for the dentate gyrus. In other words, the leftward asymmetry of the entorhinal cortex as well as the rightward asymmetry of CA1, CA2, CA3, subiculum, and also the hippocampal complex as a whole becomes significantly more pronounced as we get older.

Table 3. Pearson correlation between age and hippocampal asymmetries (absolute).

Region	Change in Magnitude	Correlation Coefficient (r)	T | df	*p*, Corrected
CA1	increase	0.09	2.5 | 720	0.013
CA2	increase	0.11	2.9 | 720	0.006
CA3	increase	0.15	4.2 | 720	<0.001
DG	not significant	0.07	1.8 | 720	0.073
Subiculum	increase	0.22	6.2 | 720	<0.001
Entorhinal	increase	0.12	3.1 | 720	0.003
Hippo	increase	0.18	4.8 | 720	<0.001

CA1, 2, 3 = cornu ammonis 1, 2, 3; DG = dentate gyrus; df = degrees of freedom.

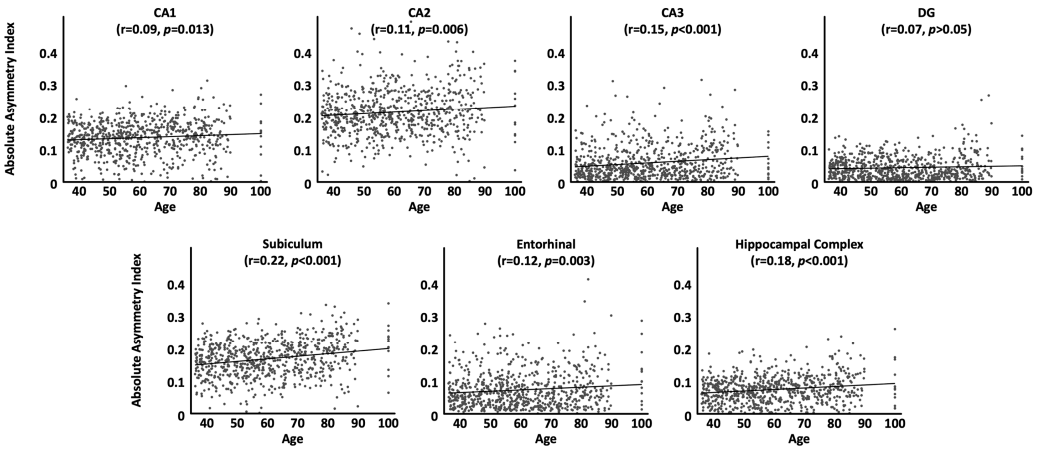

Figure 1. Associations between age and the absolute asymmetry index by subregion, adjusted for sex, handedness, TIV, and site effects. All correlation coefficients are positive, indicating an increase in asymmetry with age. Significance values are corrected for multiple comparisons.

As shown in Table 4 and Figure 2, when using the directional asymmetry index, the aforementioned significant correlations for CA2, CA3, subiculum, and the hippocampal complex as a whole were confirmed. In contrast, the significant correlations for CA1 and the entorhinal cortex were no longer significant. Conversely, the correlation for the dentate gyrus became significant.

Table 4. Pearson correlation between age and hippocampal asymmetries (directional).

Region	Change in Asymmetry | Change in Magnitude	Correlation Coefficient (r)	T | df	*p*, Corrected
CA1	not significant	0.07	1.9 | 720	0.067
CA2	rightward | increase	0.09	2.5 | 720	0.028
CA3	rightward | increase	0.06	2.3 | 720	0.034
DG	leftward | decrease	0.17	4.5 | 720	<0.001
Subiculum	rightward | increase	0.22	6.2 | 720	<0.001
Entorhinal	not significant	−0.02	0.5 | 720	0.645
Hippo	rightward | increase	0.08	2.3 | 720	0.034

CA1, 2, 3 = cornu ammonis 1, 2, 3; DG = dentate gyrus; df = degrees of freedom.

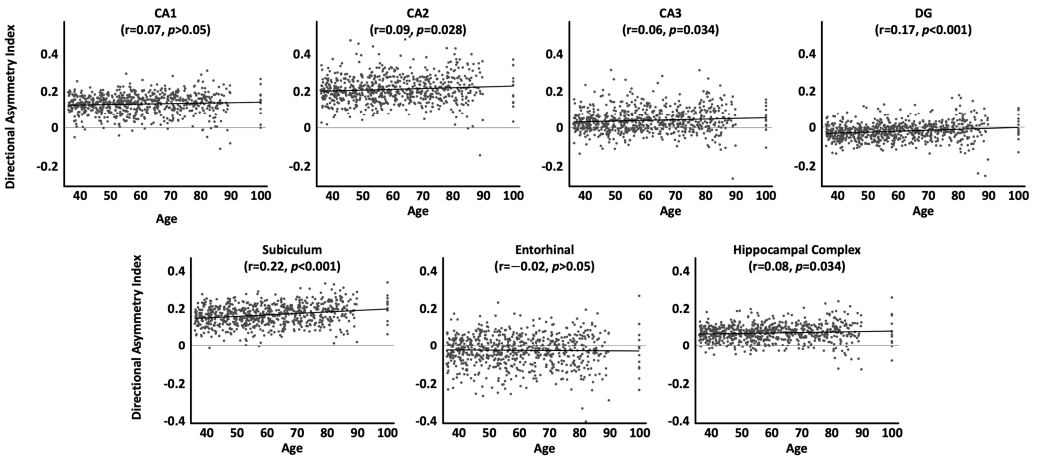

Figure 2. Associations between age and the directional asymmetry index by subregion, adjusted for sex, handedness, TIV, and site effects. Positive values denote a rightward asymmetry, negative values a leftward asymmetry. Significance values are corrected for multiple comparisons.

4. Discussion

Our study revealed a significant asymmetry in all hippocampal regions as well as significant asymmetry changes with increasing age for most hippocampal regions, except for the dentate gyrus. Significant links between asymmetry and age were positive (i.e., stronger asymmetries at an older age). This suggests that, overall, the left and the right hippocampi seem to become more different over time. In general, this conclusion is in line with findings from a previous study in 398 individuals, which revealed an increasing rightward asymmetry of the hippocampus with increasing age [24]. It also matches, at least to some degree, theories of an accelerated volume loss of the left hemisphere [11] as well as the right hemisphere [8,40]. Moreover, our current findings extend previous ones by adding insights into specific subregions (rather than the hippocampal complex as a whole), both with respect to the magnitude and the direction of asymmetry as well as the correlations between asymmetry and age.

Interestingly, when using the directional asymmetry index, the aforementioned effects pertaining to the absolute asymmetry index could not be replicated for CA1, the entorhinal cortex, or the dentate gyrus. For CA1 and the entorhinal cortex, the previously observed significant link with age was no longer significant; for the dentate gyrus, the previously observed non-significant link became significant. To understand what happened here, we should consult the plots for the directional asymmetry index (Figure 2). Taking the case of CA1 as an example, when visually inspecting the scatterplots and comparing younger ages (e.g., between 40 and 50 years) with older ages (e.g., 80–90 years), there are considerably larger leftward asymmetries as well as slightly larger rightward asymmetries later in life. So, when calculating the directional asymmetry (where leftward asymmetries are marked by negative values and rightward asymmetries by positive values), the increasingly stronger left- and rightward asymmetries over time may cancel each other out (i.e., the net change over time might appear closer to zero), at least enough so that the resulting correlation with age is not significant. In contrast, when using the absolute asymmetry index, there are only positive values regardless of whether asymmetries become more rightward or more leftward over time (i.e., the net change over time is no longer close to zero but rather substantial). As a result, the correlation with age is significant.

The differential outcomes when using the directional and absolute asymmetry index serve as a good reminder that each index has its own strengths and weaknesses: the absolute asymmetry index encodes the magnitude of the difference between the two hemispheres, but lacks information on the direction of the asymmetry, while the directional asymmetry index encodes both the magnitude and direction of asymmetry, but may obscure findings when conducting correlation analyses. The latter effect was explained above using the example of CA1 but should be considered for all subregions: as shown in the scatterplots displaying the directional asymmetry index (Figure 2), there is no single direction of asymmetry for a particular (sub)region across all individuals (albeit one direction might dominate). In our study, most (sub)regions show a rightward asymmetry on average, but there were always individuals who presented with a leftward asymmetry. If asymmetries increase with age, then it is plausible to assume that existing leftward asymmetries might increase just as existing rightward asymmetries do. Using the directional asymmetry index may then underestimate the magnitude of change over time across the sample as shifts in left- and rightward asymmetries would (at least partly) cancel each other out. This effect was also observed in the present study, where the directional asymmetry index yielded slightly different and mostly weaker associations between asymmetry and age than the absolute directional asymmetry index. If sample sizes lack the necessary statistical power, such weaker associations may manifest as non-significant effects in underpowered studies. On this note, effect sizes are small overall (see Tables 3 and 4), so the significant correlations between hippocampal asymmetry and age in our study may have been the result of our relatively large sample (N = 725).

In summary, asymmetry studies that involve correlation analyses may benefit from using the absolute asymmetry index, preferably in combination with the directional asym-

metry index. The latter is still necessary for establishing the direction of asymmetry independent of any correlation, as well as to detect any shifts in the direction of asymmetry over time or in dependence of an intervention, etc. Moreover, future longitudinal studies are needed to confirm the current cross-sectional effects and also to determine if hippocampal asymmetries—and possibly asymmetries in general—always increase over time regardless of whether they are small or large to begin with (leftward or rightward, respectively). Furthermore, given that the subregions of the hippocampal complex serve different brain functions, follow-up research is needed to explore the functional implications within the framework of brain aging, also considering the opposing asymmetries (leftward/rightward) not only across subregions, but also across individuals.

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Informed Consent Statement: Informed consent was obtained from all participants involved in the study.

Data Availability Statement: All data were obtained from the Lifespan Human Connectome Project in Aging via the National Institute of Mental Health Data Archive (NDA—https://nda.nih.gov).

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