Shared and unique heritability of hippocampal subregion volumes in children and adults

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ABSTRACT

Behavioral genetic analyses have not demonstrated robust, unique, genetic correlates of hippocampal subregion volume. Genetic differentiation of hippocampal longitudinal axis subregion volume has not yet been investigated in population-based samples, although this has been demonstrated in rodent and post-mortem human tissue work. The following study is the first population-based investigation of genetic factors that contribute to gray matter volume along the hippocampal longitudinal axis. Twin-based biometric analyses demonstrated that longitudinal axis subregions are associated with significant, unique, genetic variance, and that longitudinal axis subregions are also associated with significant shared, hippocampus-general, genetic factors. Our study's findings suggest that genetic differences in hippocampal longitudinal axis structure can be detected in individual differences in gray matter volume in population-level research designs.

1. Introduction

Work in rodents (Fanselow and Dong, 2010), non-human primates (Strange et al., 2014) and humans (Poppenk et al., 2013) conclusively demonstrates that the hippocampus differs in structure and function along its longitudinal axis. Recent work in humans suggests that hippocampal longitudinal-axis subregions also differ in their developmental trajectories (Langnes et al., 2020) and functional properties (Langnes et al., 2019) across age. The following study investigates whether longitudinal axis heterogeneity is associated with specific genetic factors, and whether these effects can be detected in living humans.

Experimental work strongly suggests that there is a genetic contribution to longitudinal axis organization in the hippocampus (Fanselow and Dong, 2010; Vogel et al., 2020; Genon et al., 2021). These studies, however, do not establish how individual differences in genetic factors relate to individual differences in hippocampal structure along the longitudinal axis. The genetic correlates of individual differences are often established using large samples of genetically related humans, such as in family-based study designs that can require hundreds of individuals, or even larger samples of genetically unrelated humans, such as in Genome Wide Association Studies (GWAS) that can require hundreds of thousands of individuals. These "population-based studies" have only recently been used to study the genetic correlates

of hippocampal subregions. Both twin and GWAS-based designs have been used to investigate the genetic correlates of gray matter volume among hippocampal transverse axis subregions (Bahrami et al., 2022; Elman et al., 2019; Patel et al., 2017), which are difficult to measure accurately in living humans (Wisse et al., 2014, 2021). In addition, one other study has investigated genetic differences in gradients of functional connectivity, myelin content, and neocortical structural covariance across the hippocampal longitudinal axis (Bayrak et al., 2021). The following study builds on this previous work by conducting the first population-based genetic study of gray matter volume along the hippocampal longitudinal axis.

As no previous population-based genetic study has assessed the heritability of gray matter volume along the longitudinal axis, it is unclear whether certain portions of the hippocampal longitudinal axis are more strongly related to genetic variables than others. Heritability is a statistical coefficient that represents the amount of variation in a phenotype (e.g hippocampal volume) that covaries with variation in a genetic profile. Family-based genetic studies, for instance, measure genetic profiles indirectly by comparing groups of genetically related individuals. Family-based studies of the hippocampus have estimated that the heritability of total hippocampal gray matter volume is roughly 80% (Elman et al., 2019; Eyler et al., 2011; Patel et al.,

2017). This means that 80% of the variability in total hippocampal volume among the population can be explained by genetic variation within and between families. Thus, genetic variables seem to explain most of the variance in hippocampal volume. In family-based genetic studies of the hippocampus, systematic environmental effects have, to our knowledge, never explained a statistically significant proportion of variance in gray matter volume. This finding is in stark contrast with experimental findings that suggest environmental experiences can exert causal effects on hippocampal gray matter (Maguire et al., 2000, 2006; McEwen, 2012). The friction between these research traditions may potentially be resolved by incorporating hippocampal longitudinal axis structure into population-based genetic studies. There is reason to hypothesize, for instance, that the magnitude of heritability in gray matter volume may vary along the longitudinal axis. For instance, recent work suggests that the anterior hippocampus may be more sensitive to the effects environmental stressors than the posterior hippocampus (Botdorf et al., 2022). These findings suggest that the anterior hippocampus may have a lower heritability coefficient, and that systematic environmental factors may account for more variance in anterior hippocampal volume relative to posterior regions.

As no previous population-based genetic study has assessed the heritability of gray matter volume along the longitudinal axis, it is also unclear whether the same genetic factors influence gray matter volume along the hippocampal longitudinal axis or whether different regions of the hippocampal longitudinal axis are associated subregion-specific genetic factors. There are several lines of evidence suggesting that the genetic factors influencing gray matter volume may differ along the hippocampal longitudinal axis. Recent work using samples from post-mortem tissue in the Allen Human Brain Atlas suggests that gene expression in the hippocampus varies along a longitudinal gradient (Vogel et al., 2020). This database includes numerous tissue samples from various positions along the hippocampal longitudinal axis, and Vogel et al. demonstrated that the position of each sample along the hippocampal longitudinal axis could be predicted from a LASSO-PCR algorithm using only gene expression data (Vogel et al., 2020). Furthermore, Vogel et al. demonstrated that the most influential gene sets within this model exhibited varying degrees of transcript expression along the hippocampal longitudinal axis. Many of these gene sets are implicated in processes that determine hippocampal structure specifically (Vogel et al., 2020) which suggests that genetic variation may relate to gray matter volume in population-based samples. It is unclear, however, whether genetic differences in hippocampal longitudinal axis subregions produce effects that are strong enough to be observed in population-based studies of living humans. The current study builds on this work by investigating whether individual differences in gray matter volume along hippocampal longitudinal axis are associated with unique, subregion-specific, genetic factors

Lastly, existing work on the genetics of the hippocampus suggests that the genetic architecture of hippocampal volume may differ between children and adults. GWAS of hippocampal gray matter volume demonstrate statistically significant effects for SNPs related to oxidative stress and glucocorticoid-mediated activity in the hippocampus (van der Meer et al., 2020), and for gene-sets related to sexual reproduction and gamete generation (Bahrami et al., 2022). Humans reach sexual maturity during adolescence, and this developmental period also comes with significant increases in psychosocial stress (Blakemore and Choudhury, 2006). Thus, pre-adolescent children have yet to experience the neurobiological phenomena that may partially mediate the relationship between genetic variability and individual differences in hippocampal volume. This may lead to potentially significant differences in the genetic constituents of hippocampal volume between pre-adolescent children and post-adolescent adults. Age-related changes in heritability have been demonstrated for many behavioral phenotypes (e.g body-mass index, intelligence quotient), although this phenomenon is less robust with neuroimaging studies perhaps due to the difficulty of collecting large samples (for examples see Batouli et al. (2014), Le Grand et al. (2021) and Swagerman et al. (2014)). Age-related differences in the heritability of behavioral phenotypes have been interpreted as evidence of the influence of gene-by-environment interactions (Beam and Turkheimer, 2013; Briley and Tucker-Drob, 2017) and age-related differences in gene expression (Bouchard, 2013). As the hippocampus is both highly sensitive to the environment (Maguire et al., 2000, 2006; McEwen, 2012) and highly heritable (Elman et al., 2019; Eyler et al., 2011; Patel et al., 2017), it is reasonable to hypothesize that gene-by-environment interactions may produce age-related changes in the heritability of hippocampal volume. Adolescence has also been shown to involve changes in neurotransmitter availability in hippocampal circuits, which may indicate that the genetic correlates of hippocampal volume may exhibit developmental changes in expression (Lavenex et al., 2011). In summary, there is ample evidence to suggest that there may be age-related differences in the heritability of hippocampal volume, although this phenomenon has been difficult to uncover in extant neuroimaging data.

The following study will utilize data collected from two population-based studies of monozygotic (MZ) and dizygotic (DZ) twins, the Adolescent Brain and Cognitive Development study and the Human Connectome Project – Young Adult sample, in order to investigate three primary aims. First, this study will investigate differences in the magnitude of genetic influence on hippocampal longitudinal axis subregions. Differences in the magnitude of genetic influence between children and adults for a specific subregion will be investigated using both univariate and multivariate twin-based genetic models. Secondly, this study will investigate whether the genetic influences on hippocampal longitudinal axis subregions are driven by primarily common, hippocampus general, genetic factors, or whether the genetic influences on hippocampal longitudinal axis subregions are driven by unique, subregion-specific, genetic factors. Lastly, this study will investigate differences in the univariate and multivariate genetic influences on hippocampal longitudinal axis subregions between children and adults. These three aims represent important gaps in current knowledge of genetic influences on the human hippocampus; given that twin-based studies are the most statistically powered design to detect aggregated genetic components, and the fact that the following study utilizes an unprecedented sample size to study the genetic components of hippocampal volume in living humans (883 twin pairs), the following study represents the most statistically-powered investigation of these existing knowledge gaps to date.

2. Materials and methods

2.1. Participants

The sample of children used for this study was comprised of MZ and DZ twin pairs within the Adolescent Brain and Cognitive Development (ABCD) study (ABCD Twin Hub; Iacono et al., 2018). The sample of adults used for this study was comprised of MZ and DZ twin pairs within the WU-Minn Human Connectome Project (S-1200 release) (HCP; Van Essen et al., 2013). Twin pairs from both samples were recruited using the respective birth registries for the years 2006–2008 for each state. This study only utilized data from twin pairs with genotype-confirmed zygosity status. The final sample for this study consisted of 883, same-sex twin pairs: the child sample analyzed for this study consisted of 666 twin pairs (Monozygotic (MZ) = 310; Dizygotic (DZ) = 356), and the adult sample consisted of 217 (MZ = 138; DZ = 79). The ABCD sample includes 47 DZ twin pairs that do not have matching sex and these participants were not included in the final sample for this study. The average age of the ABCD sample was 10.1 years, and ranged from 9–10.9 years old. The average age of the HCP sample was 29.3 years old, and ranged from 22–36 years old. Of the entire ABCD sample, 350 pairs identified as Caucasian, 103 identified as African American, 126 identified as Hispanic, 17 identified as Asian, and 69 as a race different than those listed. One twin pair

did not know or did not report their race. Of the entire HCP sample, 182 pairs identified as Caucasian, 22 identified as African American, 8 identified as Asian/Native Hawaiian/or Pacific Islander, 3 identified as more than one race, and 2 did not know or did not report their race.

2.2. MRI acquisition and processing

Structural MRI scans for ABCD participants are collected using harmonized pulse sequences on one of seven possible MRI scanner models. The acquisition protocol included both a 3D MPRAGE T1- weighted volume (TE = 2–2.9 ms, TR = 6.31 – 2500 ms, T1 = 1060 ms, flip angle = 8 degrees, FOV = 256 × 256, resolution = 1 mm isotropic, slice thickness, slices = 176–225) and a T2- weighted volume (TE = 60–565 ms, FOV = 256 × 256, resolution = 1 mm isotropic, slices = 176–225). ABCD Twin hub participants used for this study were scanned using Siemans Prisma (N = 269), Siemans Prisma fit (N = 222) Philips Achieva dStream (N = 6), Phillips Ingenia (N = 102), and SIGNA Creator (N = 1). All structural MRI scans for HCP twin pairs were collected with a Siemens 3T Skyra scanner with a 32-channel head coil. The acquisition protocol included a 3D MPRAGE T1-weighted volume (TE = 2.14 ms, TR = 2400 ms, TI = 1000 ms, flip angle = 8 degrees, FOV = 224 × 224, in-plane resolution = 0.7 × 0.7 mm, slice thickness = 0.7 mm, slices = 256). The T1 and T2-weighted structural scans used for the child sample of this study were processed by the Developmental Cognition and Neuroimaging (DCAN) labs as part of the ABCD-BIDS Community Collection (ABCC). These methods are described in detail at the following webpage (https://collection3165.readthedocs.io/en/stable/release_notes/). Subcortical segmentations for both HCP and ABCD Twin hub data were obtained by using automated segmentation tools to isolate subcortical structures (Fischl et al., 2002). Segmentation of hippocampal longitudinal subregions was conducted using both T1 and T2 images from the Freesurfer v7.0 automated hippocampal subfield segmentation tool (Iglesias et al., 2015). This tool employs a probabilistic atlas built from a combination of 7T ultra-high field resolution, 0.13 mm^3, ex vivo, MRI scans, which were used to isolate hippocampal substructures, and a separate dataset of in vivo T1-weighted, 1 mm^3, MRI scans of the whole brain, which were used to isolate the total hippocampus from surrounding neural structures (e.g entorhinal cortex, amygdala). ABCD and HCP structural data has been previously inspected for movement, acquisition inhomogeneities, and image artifacts. Only images that received passing quality control scores were included in the following analyses. Detailed information on HCP quality control procedures are detailed at Marcus et al. (2013). Data dictionaries for ABCD quality control parameters can be viewed and downloaded at (https://nda.nih.gov/data_structure.html?short_name=abcd_imgincl01).

2.3. Biometric modeling

Prior to conducting the primary analyses for this study, bivariate genetic models were used to determine the utility of aggregating hippocampal volume estimates across hemispheres. In line with previous work (Elman et al., 2019; Eyler et al., 2011), all regions of the hippocampus shared high degrees of genetic covariation across hemispheres for both male and female participants in the ABCD and HCP samples (i.e the confidence interval for the genetic correlation included 1; results shown in supplementary materials). This suggests there are little to no unique sources of genetic variance for the hippocampus of one hemisphere relative to the other. As a result, hippocampal volume estimates were averaged across hemispheres for all primary analyses presented in this manuscript.

Prior to conducting all univariate and multivariate biometric modeling, hippocampal gray matter volume estimates were transformed using the following order of operations. First, all hippocampal gray matter estimates were standardized by subtracting the mean and dividing by the standard deviation. Second, using linear regression, hippocampal

gray matter estimates were transformed into residual scores that eliminated sources of covariance with sex and age. These transformations were performed within the ABCD and HCP samples separately, but were not performed separately for male and female participants as the linear relationship between age and hippocampal subregion volume was not moderated by sex for any of the hippocampal subregions studied in either the ABCD (Head: $B = 0.01$; $p = 0.07$; Body: $B = 0.00$; $p = 0.97$; Tail: $B = -0.01$; $p = 0.39$) or HCP sample (Head: $B = 0.01$; $p = 0.62$; Body: $B = -0.02$; $p = 0.50$; Tail: $B = 0.02$; $p = 0.45$).

Univariate biometric models were used to investigate the magnitude of genetic influence across hippocampal subregions. Biometric models attribute total phenotypic variance to three possible sources, primarily based on the differences in phenotypic correlation within MZ and DZ pairs. Additive genetic variance (denoted by A) represents the latent influence of segregating loci that are typically shared 100% and 50% identical-by-descent by members of MZ and DZ twin pairs respectively. Evidence for A arises when the MZ correlation is greater than the DZ correlation. Individual-specific environmental variance (denoted by E) includes person-specific factors and any influences of measurement error; E-associated variance is, in contrast to A, not shared between members of MZ or DZ twin pairs. Evidence for E arises from an MZ correlation that is statistically different from 1.0. While A and E are typically included as variance components in most biometric models, the third source of variance is selected based on the pattern of MZ and DZ twin pair correlations. Assuming that the influence of A as the sole source of twin similarity would result in a DZ correlation that is approximately half the magnitude of the MZ correlation, the third variance component is selected to be an additional, non-additive source of genetic similarity (denoted by D, for dominance genetics, or the interacting effects of loci) when the DZ correlation is considerably lower than half the MZ correlation. By contrast, a familial source of environmental variance (denoted by C, for twin-common environment) is modeled as the third variance component if, in contrast, the DZ correlation is greater than half the MZ correlation. Once total genetic variance has been attributed to one-to-three of these sources, narrow sense heritability is equal to $\frac{A}{A+C+E}$, or the proportion of total variance due to additive genetic variance (in the presence of D, broad and narrow sense heritability can also be estimated) (Neale and Cardon, 1992). In the results section of this manuscript, heritability refers to either narrow sense or broad sense heritability depending on the context. Subregions that are modeled as ADE are explicitly noted, and the heritability estimates of these regions represent broad sense heritability.

Multivariate models were used to investigate shared and unique sources of genetic variation across hippocampal subregions. Fig. 1 demonstrates a simplified visual depiction of the differences between univariate genetic models, and the primary multivariate model used for this study. Multivariate models build from the general univariate framework in order to decompose sources of covariation between phenotypes into shared sources of genetic and environmental variability. This study employed an Independent Pathway model in order to draw inferences regarded shared and subregion specific sources of genetic variance across hippocampal subregions. Independent Pathway models provide estimates of shared genetic and environmental effects on each hippocampal subregion, and also provide estimates of unique, subregion-specific genetic and environmental effects. Genetic and environmental effects that are unique to specific subregions will be referred to as "subregion-specific" effects, so as to minimize confusion between these parameter estimates and the estimates for unique environmental effects (E). Similarly, genetic and environmental that are shared between hippocampal subregions will be referred to as "shared" effects, so as to minimize confusion between these parameter estimates and the estimates of common environmental effects (C). Although an Independent Pathway model was used for all inferences within this manuscript, model comparisons that employed other multivariate parameterizations are displayed in the supplementary materials.
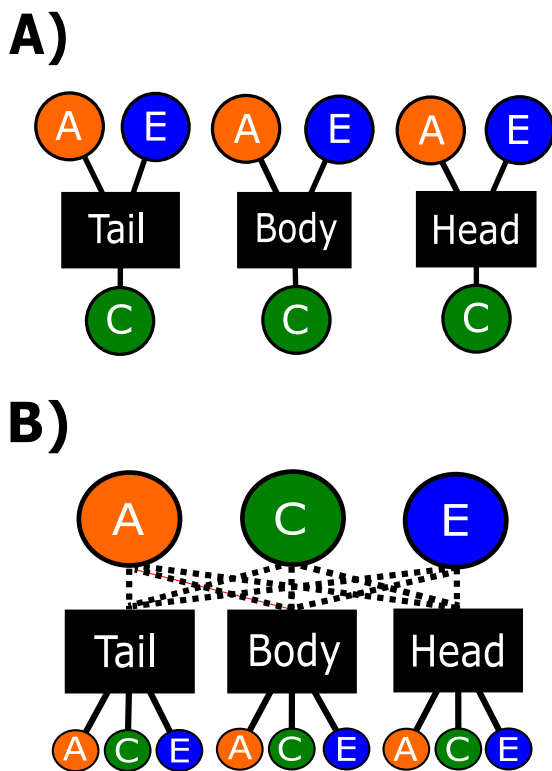
A)

B)

Fig. 1. Generalized depiction of univariate and multivariate models considered for this study. Shared sources of variation between variables are displayed with dashed lines: (A) univariate models with three separate sets of parameters for hippocampal tail, hippocampal body, and hippocampal head. In cases where MZ correlations are greater than twice that of DZ correlations, common environment (C) effects are replaced with those of dominance genetics (D); (B) Independent Pathway models include sources of shared variation between hippocampal subregions, and sources of subregion-specific variation that are unique to each hippocampal subregions.

2.4. Model selection

Genetic and environmental effects were estimated for four groups of participants: male and female participants in the ABCD sample and male and female participants in the HCP sample. Briefly, the best fitting models were constructed, in both the univariate and multivariate case, according to the following steps: first, a "full model" was fit, which included separate parameter values for each group in the data. Thus, for a univariate ACE model, variability in hippocampal gray matter was estimated with separate sets of parameters for the additive genetic (A) effects, common environment (C) effects, and unique environmental (E) effects for each of the four groups (male and female participants in the ABCD and HCP samples). ACE models were compared against ADE models for each specific group. "Full models" were compared against a "saturated model", which estimates means and variances for MZ and DZ twins separately, and does not include any latent variable parameters. If genetic and environmental latent variables can successfully explain hippocampal subregion volumes among both MZ and DZ twin pairs, then the "full model" should not demonstrate a statistically significant loss of fit relative to the "saturated model". In both the multivariate and univariate case, if an ADE model provided a better fit relative to the ACE model, then an ADE model was used for that group. In all cases, model comparisons were conducted based on differences in the log of the likelihood of the model ($-2LL$) and the resulting p-value from likelihood-ratio tests. Fit metrics for all model comparison analyses are presented in the supplementary materials, along with a relatively more thorough explanation of the model selection process.

3. Results

3.1. Phenotypic correlations

Fig. 2 visually demonstrates the phenotypic patterns of correlations across twin pairs in both the ABCD and HCP samples and in both male and female participants. Scatter plots showing the data that produced these correlations are shown in the supplementary materials ("phenotypic correlations" section). First, this figure demonstrates correlations between different hippocampal subregions within individual members of a twin pair, which are denoted by correlations between hippocampal subregions that are labeled with the same number (e.g "1" or "2"). These correlations show that, in both MZ and DZ pairs, correlations in gray matter between hippocampal longitudinal axis subregions are lower for subregions that are further away from one another. In all four groups, and for each member of MZ and DZ twin pairs, the hippocampal head correlates more with the hippocampal body relative to the correlation between the hippocampal head and the hippocampal tail. Thus, no matter the age or sex of the participant or their twin type, the magnitude of covariation between hippocampal subregions increases when longitudinal axis subregions are closer to one another.

Fig. 2 also demonstrates that the gray matter volume of hippocampal subregions tends to correlate to a greater extent in MZ twins relative to DZ twins. This phenomenon emerges from considering cross-twin correlations, in which the gray matter estimate from a hippocampal subregion in the first member of the twin pair (e.g "Head1") is correlated with a hippocampal subregion from the second member of the twin pair (e.g "Head2"). In all four groups, the cross-twin correlations between hippocampal subregions tend to be greater in MZ twins relative to DZ. This can be demonstrated by considering the cross-twin correlations in hippocampal head volume: the correlation in hippocampal head volume between the first ("Head1") and second ("Head2") twin among MZ, female, twins in the ABCD sample is 0.86, while the corresponding correlation among the DZ twins of this group is 0.51. Large differences in cross-twin correlations are consistent with a strong genetic contribution to phenotypic variability. Certain hippocampal subregions exhibit cross-twin correlations that are more than twice the magnitude in MZ twins relative to DZ twins. For instance, among male participants in the ABCD sample, gray matter volume from the hippocampal tail exhibits an MZ cross-twin correlation of 0.82, while the corresponding cross-twin correlation for the DZ twins is 0.34. MZ cross-twin correlations that are more than twice the magnitude of DZ cross-twin correlations are consistent with additional genetic dominance effects.

3.2. Biometric modeling results

Univariate analyses investigated the contribution of genetic and environmental factors to variance in the gray matter volume of hippocampal longitudinal axis subregions. In univariate analyses, sources of covariation between hippocampal subregions are not examined. Table 1 displays standardized parameter estimates from the best fitting univariate models for the hippocampal tail, hippocampal body, and hippocampal head. Each parameter estimate represents a percentage of total variance explained. For each hippocampal longitudinal axis subregion, genetic factors explained the dominant proportion of variance in gray matter volume (i.e greater than 75% for all groups). Common environmental effects accounted for approximately 12% of gray matter volume variance for the hippocampal head in the ABCD male, ABCD female, and HCP male sample. These environmental effects were not statistically significant based on likelihood-ratio tests ($\Delta-2LL$ = 2.52; P value = 0.11). All other univariate models replaced common environmental effects with dominance genetic components.

Multivariate relationships between hippocampal subregions were assessed with an Independent Pathway model that included 20 parameters (see supplementary materials for model selection details).
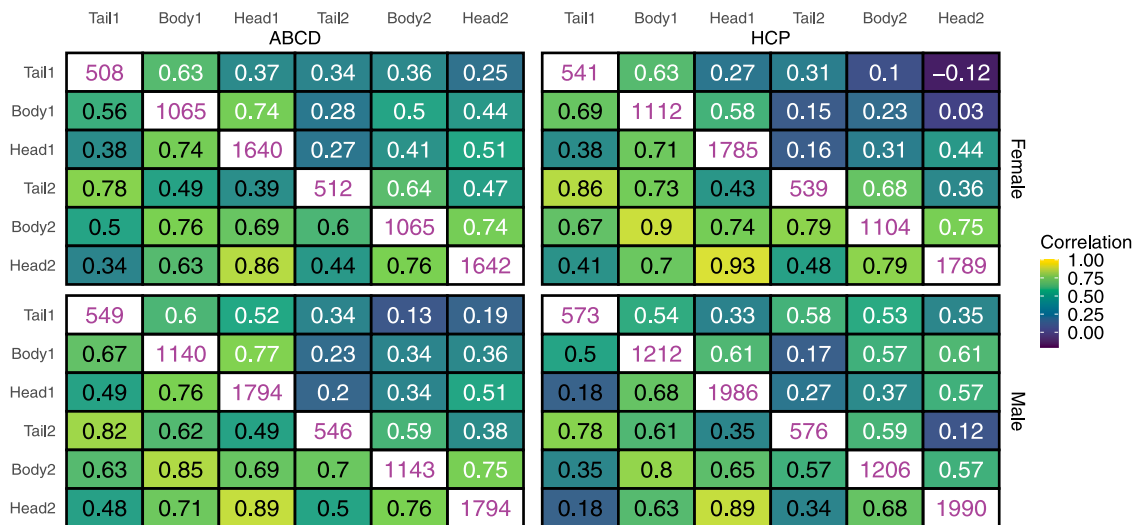
Phenotypic Means and Correlations

Fig. 2. Means and phenotypic correlations among hippocampal longitudinal axis subregions. MZ twin correlations are displayed in the lower triangle with black font. DZ twins are displayed in the upper triangle in white font. The mean gray matter volume for each longitudinal axis subregion is shown on the diagonal in purple font. Means were not computed separately for MZ and DZ twin pairs.

Table 1
Univariate Model Parameter Estimates.

Variance component	Group	% Variance explained (CI)		
		Tail	Body	Head
Heritability	ABCD Female	0.81 (0.79 to 0.83)	0.76 (0.70 to 0.86)	0.76 (0.60 to 0.87)
	ABCD Male	0.81 (0.79 to 0.83)	0.86 (0.83 to 0.89)	0.76 (0.60 to 0.87)
	HCP Female	0.81 (0.79 to 0.83)	0.88 (0.85 to 0.91)	0.92 (0.90 to 0.94)
	HCP Male	0.81 (0.79 to 0.83)	0.82 (0.77 to 0.86)	0.76 (0.60 to 0.87)
		Tail	Body	Head
Dominance Genetics*/Common Environment[†]	ABCD Female	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.12 (0.00 to 0.27)[†]
	ABCD Male	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.12 (0.00 to 0.27)[†]
	HCP Female	0.00 (0.00 to 0.00)	0.88 (0.85 to 0.91)*	0.00 (0.00 to 0.00)
	HCP Male	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.12 (0.00 to 0.27)[†]
		Tail	Body	Head
Unique Environment	ABCD Female	0.19 (0.17 to 0.21)	0.24 (0.14 to 0.30)	0.12 (0.10 to 0.14)
	ABCD Male	0.19 (0.17 to 0.21)	0.14 (0.11 to 0.17)	0.12 (0.10 to 0.13)
	HCP Female	0.19 (0.17 to 0.21)	0.12 (0.09 to 0.15)	0.08 (0.06 to 0.10)
	HCP Male	0.19 (0.17 to 0.21)	0.18 (0.14 to 0.23)	0.12 (0.10 to 0.13)

Parameter outputs from this model are shown in Table 2, and are displayed as proportions of variance. Visual depictions of these effects are demonstrated in Fig. 3A for the broad sense heritability (the sum of additive (A) and dominance (D) genetic components), and Fig. 3B for the unique environmental effects. Based on likelihood ratio tests, there were no significant differences in the magnitudes of heritability between the hippocampal tail, hippocampal body, and hippocampal head among any of the participant groups.

As shown in Table 2, the multivariate models demonstrated significant shared broad sense heritability (the sum of additive and dominance genetic components) for all three hippocampal longitudinal subregions across all four groups. The variance accounted for by this shared broad sense heritability component was significantly stronger for the body and the head compared to the tail. There were also significant shared unique environmental effects for all three longitudinal subregions, most strongly for the body compared to the head and tail.

At the same time, multivariate models provided several indications that hippocampal longitudinal axis subregions are associated with subregion-specific genetic components. Likelihood ratio tests for each of these statistical tests can be viewed in supplementary table 9. As can be seen in Table 2, the hippocampal tail had statistically significant, subregion-specific broad sense heritability (additive and dominance genetic components) in all four groups. However, the hippocampal head only showed statistically significant subregion-specific

broad sense heritability in both male and female ABCD participants, and the hippocampal body only in male ABCD participants. Among HCP male participants, there were additional signs that hippocampal longitudinal axis subregions were associated with differential genetic factors. In particular, the hippocampus general, shared additive genetic factor had no significant path estimate on the hippocampal tail in HCP male participants. Thus, shared additive genetic components among HCP male participants do not represent a total hippocampal additive genetic factor but instead represent a hippocampal head and body additive genetic factor. In addition, the total hippocampal, common dominance genetic factor had no significant path estimates on the hippocampal head. Therefore, the common dominance genetic components among HCP male participants do not represent a total hippocampal dominance genetic component but instead represent a genetic component that is specific to the hippocampal body and hippocampal tail. Each hippocampal longitudinal axis subregion was associated with statistically significant, subregion-specific, unique environmental components. While there were no statistically significant subregion-specific, unique environmental effects associated with the hippocampal body, the hippocampus general, unique environmental effects predominantly explained variance in the hippocampal body, with minimal path estimates on the hippocampal tail and hippocampal head.

There were a number of statistically significant differences in both univariate and multivariate genetic and environmental effects between
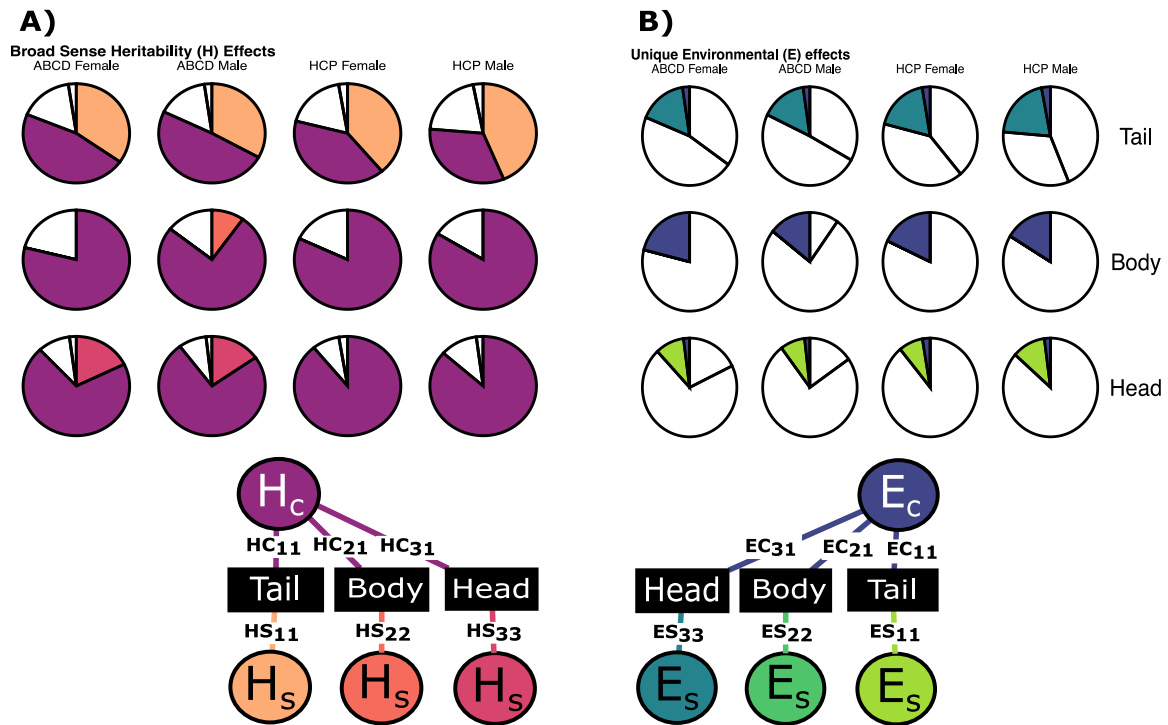
Fig. 3. Genetic and environmental effects from the full multivariate ADE IP model. In each case, subregion specific parameters are denoted with an "S" subscript, while total hippocampal factors are denoted with a "C" subscript. Parameters are represented as unstandardized, squared path coefficients (e.g genetic variance specific to hippocampal tail: $HS_{11} * HS_{11}$), which are then divided by the phenotypic variance (e.g total hippocampal tail variance: $(HS_{11} * HS_{11}) + (HC_{11} * HC_{11}) + (ES_{11} * ES_{11}) + (EC_{11} * EC_{11})$). (A) Broad sense heritability effects are displayed as proportions of total variance explained. Each piechart reflects the same data as is represented in B, but with unique environmental effects whitened out. Broad sense heritability represents the sum of additive and dominance genetic components; (B) Unique environmental effects are displayed as proportions of total variance explained. Each piechart reflects the same data as is represented in A, but with broad sense heritability effects whitened out.

4. Discussion

As previously mentioned, this study investigated three primary aims. First, this study investigated whether gray matter volume estimates among hippocampal longitudinal axis subregions are associated with significant differences in the magnitudes of their genetic effects. Univariate and multivariate biometric models demonstrated that there are no significant differences in the heritability of gray matter volume between different hippocampal longitudinal axis subregions. This was demonstrated with univariate models, which showed largely overlapping confidence intervals for heritability estimates among hippocampal longitudinal axis subregions, and multivariate models, which showed no significant differences in the heritability of hippocampal longitudinal axis subregions based on likelihood ratio tests. While the heritability estimate for the hippocampal head was somewhat larger for HCP female participants relative to other groups, this effect was driven by the replacement of common environmental effects with genetic dominance effects for HCP females. In other words, hippocampal head volume for HCP females was modeled with only one environmental parameter (E), while hippocampal head volume for other groups was modeled with two environmental parameters (C and E).

In addition, this study investigated the degree to which heritability estimates of hippocampal longitudinal axis subregions are driven by subregion-specific genetic components. Previous studies have investigated this question using post-mortem human data, as well as data from hippocampal microstructure, structural covariance, and connectivity

gradients in living humans. This study demonstrated, using multivariate independent pathway models, that individual differences in gray matter volume along the hippocampal longitudinal axis are associated with statistically significant subregion-specific genetic components, although these effects differed across male and female participants in HCP and ABCD samples. We demonstrated that (1) significant, subregion-specific genetic components contribute to gray matter volume in the hippocampal tail across male and female children and adults; (2) that there are significant, subregion-specific genetic components that contribute to gray matter volume in the hippocampal head among male and female children; and (3) that significant subregion-specific, dominance genetic effects contribute to gray matter volume in the hippocampal body among male children.

The findings from this study provide the first estimates of genetic influence on individual differences in gray matter volume along the longitudinal axis. These findings will likely have practical implications, as longitudinal-axis subregion-specific, gray matter volume reductions are observed in mental disorders (McHugo et al., 2018, 2020; Sahakyan et al., 2021) and in individuals exposed to environmental adversity (Botdorf et al., 2022). We are not the first study to show meaningful genetic differences along the hippocampal longitudinal axis, however we provide the first indications that genetic differences along the hippocampal longitudinal axis can be observed in individual differences in gray matter volume among living humans using non-invasive imaging methods. Our study's results may help establish the contribution of genetic variables to subregion-specific gray matter volume reductions that are observed in the context of psychopathology and environmental adversity. The practical implications of our study's findings will likely be indirect, however, as the estimates from population-based genetic studies are influenced by sample-specific contextual variables (Harden, 2021; Rimfeld et al., 2018), which may not generalize to other samples.

Table 2
Independent pathway ADE parameter estimates.

Variance component	Group	Estimate(CI)		
		Shared Hippocampal Effects		
		Tail	Body	Head
Additive Genetics	ABCD Female	0.22 (0.19 to 0.27)	0.67 (0.58 to 0.76)	0.70 (0.62 to 0.81)
	ABCD Male	0.22 (0.19 to 0.27)	0.64 (0.56 to 0.74)	0.75 (0.68 to 0.84)
	HCP Female	0.11 (0.07 to 0.17)	0.40 (0.34 to 0.48)	0.88 (0.86 to 0.90)
	HCP Male	0.00 (0.00 to 0.00)	0.40 (0.34 to 0.48)	0.88 (0.86 to 0.90)
		Tail	Body	Head
Dominance Genetics	ABCD Female	0.25 (0.21 to 0.29)	0.12 (0.05 to 0.22)	0.00 (0.00 to 0.00)
	ABCD Male	0.25 (0.21 to 0.29)	0.11 (0.05 to 0.21)	0.00 (0.00 to 0.00)
	HCP Female	0.29 (0.23 to 0.34)	0.42 (0.36 to 0.48)	0.00 (0.00 to 0.00)
	HCP Male	0.32 (0.27 to 0.37)	0.42 (0.36 to 0.48)	0.00 (0.00 to 0.00)
		Tail	Body	Head
Unique Environment	ABCD Female	0.02 (0.01 to 0.03)	0.21 (0.15 to 0.25)	0.02 (0.01 to 0.03)
	ABCD Male	0.02 (0.01 to 0.03)	0.14 (0.11 to 0.17)	0.02 (0.01 to 0.02)
	HCP Female	0.03 (0.02 to 0.04)	0.18 (0.12 to 0.21)	0.02 (0.01 to 0.03)
	HCP Male	0.03 (0.02 to 0.05)	0.18 (0.12 to 0.21)	0.02 (0.01 to 0.03)
		Tail	Body	Head
Broad Sense Heritability	ABCD Female	0.47 (0.43 to 0.54)	0.79 (0.75 to 0.85)	0.70 (0.62 to 0.81)
	ABCD Male	0.47 (0.43 to 0.54)	0.76 (0.71 to 0.81)	0.75 (0.68 to 0.84)
	HCP Female	0.40 (0.35 to 0.45)	0.82 (0.79 to 0.88)	0.88 (0.86 to 0.90)
	HCP Male	0.32 (0.27 to 0.37)	0.82 (0.79 to 0.88)	0.88 (0.86 to 0.90)
		Subregion-Specific Effects		
		Tail	Body	Head
Additive Genetics	ABCD Female	0.34 (0.29 to 0.38)	0.00 (0.00 to 0.00)	0.18 (0.08 to 0.26)
	ABCD Male	0.34 (0.29 to 0.38)	0.00 (0.00 to 0.00)	0.15 (0.07 to 0.21)
	HCP Female	0.39 (0.33 to 0.44)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)
	HCP Male	0.44 (0.39 to 0.49)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)
		Tail	Body	Head
Dominance Genetics	ABCD Female	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)
	ABCD Male	0.00 (0.00 to 0.00)	0.10 (0.05 to 0.14)	0.00 (0.00 to 0.00)
	HCP Female	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)
	HCP Male	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)
		Tail	Body	Head
Unique Environment	ABCD Female	0.16 (0.14 to 0.17)	0.00 (0.00 to 0.00)	0.10 (0.09 to 0.11)
	ABCD Male	0.16 (0.14 to 0.17)	0.00 (0.00 to 0.00)	0.08 (0.07 to 0.09)
	HCP Female	0.18 (0.16 to 0.20)	0.00 (0.00 to 0.00)	0.10 (0.09 to 0.11)
	HCP Male	0.21 (0.18 to 0.22)	0.00 (0.00 to 0.00)	0.10 (0.09 to 0.11)
		Tail	Body	Head
Broad Sense Heritability	ABCD Female	0.34 (0.29 to 0.38)	0.00 (0.00 to 0.00)	0.18 (0.08 to 0.26)
	ABCD Male	0.34 (0.29 to 0.38)	0.10 (0.05 to 0.14)	0.15 (0.07 to 0.21)
	HCP Female	0.39 (0.35 to 0.44)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)
	HCP Male	0.44 (0.39 to 0.49)	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)

This study found a number of statistically significant differences in the heritability of specific subregions between children and adults, and between male and female participants. Across age and sex, the pattern of statistically significant differences did not appear to follow any systematic pattern of which we are aware. These findings, however, should be interpreted in the context of other studies that investigated age related differences in the genetics of the hippocampus, and future studies that might investigate sex related differences. A recent GWAS of gray matter volume in hippocampal subregions has demonstrated mixed results regarding the influence of age-specific factors on estimated genetic effects (Bahrami et al., 2022). Our results provide additional context to these findings, by demonstrating that the genetic correlates of hippocampal gray matter differ between children and adults. Further, adolescence and young adulthood has been shown to be a dynamic period of white matter change in the hippocampus, and age-related changes in the functional properties of the hippocampus have also been shown across development (Langnes et al., 2019; Conley et al., 2021). Thus, age-related changes in the genetic correlates of hippocampal properties may be more readily observed for other features of the hippocampus, like white-matter and BOLD response, rather than gray matter volume. While our findings also demonstrated several statistically significant differences in hippocampal longitudinal axis heritability between male and female participants, it is unclear to what extent these findings reflect known neural mechanisms with significant genetic and environmental determinants.

This study had several limitations. First, gray matter along the hippocampal longitudinal axis was separated into three discrete subregions. While existing work demonstrates the validity of these subregions, other work suggests that hippocampal longitudinal axis heterogeneity is expressed continuously rather than discretely (Vogel et al., 2020). Thus, our segmentation of hippocampal gray matter into discrete longitudinal axis subregions may have biased our results. Secondly, this study investigated age-related differences in the heritability of hippocampal subregions using a between-subjects design. A within-subjects design would likely provide a more sensitive exploration of age-related differences in hippocampal genetics, as this design would allow us to test the degree to which the genetic components of hippocampal gray matter are related to one another throughout adolescent development. Third, while this study provides the largest twin-based study of hippocampal genetics, our sample size was nevertheless underpowered to detect the effects of the common environment. Lastly, the age range of our sample size may not have been optimal for detecting developmental differences in the heritability of hippocampal gray matter volume. The child sample for our study comprised children ages 9–11, and the adult sample for our study comprised adults 22–36. Thus, our study was best able to detect changes in the heritability of hippocampal gray matter volume associated with adolescent development. Existing work suggests, however, that hippocampal gray matter volume is relatively stable throughout adolescence, and undergoes more dynamic changes in early-to-middle childhood (Lavenex and

Banta Lavenex, 2013). Thus, if we had an even younger sample, we might see more evidence of age-related differences in the degree of unique versus shared genetic variance in hippocampal subregions.

There is a possibility that genetic influences on hippocampal volume may correlate with biases in the hippocampal segmentation algorithm. For instance, Freesurfer-based hippocampal segmentation exhibits an overestimation bias for hippocampi with smaller volumes (Schmidt et al., 2018). In this case, genetic variance would be indistinguishable from variance that emerges from bias. We do not believe such hypothetical factors can explain the effects from trivariate models. First, smaller regions (e.g the hippocampal tail) are not more or less heritable than larger regions (e.g the hippocampal head). Thus, it is unlikely that genetic variance in hippocampal subregion volume correlates with size-based bias. Second, subregion-specific variance is, by definition, uncorrelated with hippocampus general genetic variance. Thus, it is unlikely that subregion-specific genetic variance correlates with segmentation biases that manifest across the whole hippocampus. In order for hippocampal segmentation bias to account for our findings, this bias would have to (a) affect certain subregions more than others; (b) affect MZ twins to a greater extent than DZ twins; and (c) be correlated across MZ twins. While genetic variance may be correlated with other forms of bias in the hippocampal segmentation algorithm, we are unaware of any such documented biases in the longitudinal axis segmentation protocol that satisfy all three of these conditions. We hope that scatter plots of our hippocampal segmentation data, which are located in the supplementary materials, may allay any further concerns.

This study provides evidence that genetic heterogeneity along the hippocampal longitudinal axis is evident in gray matter measurements from human, population-based, samples. The collection of univariate and multivariate analyses conducted as part of this study demonstrate that gray matter measurements from structural MRI yield statistically significant effects that appear to be driven by substantive genetic differences between hippocampal longitudinal axis subregions. While existing work has demonstrated genetic differences along the hippocampal longitudinal axis in rodents and human post-mortem tissue, this is the first study to demonstrate genetic differences in a human population-based sample. In short, our study's results provide some indication that genetically-based individual differences in hippocampal longitudinal axis structure may be observable using non-invasive neuroimaging in living humans.

CRediT authorship contribution statement

Jacob G. Pine: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Arpana Agrawal:** Formal analysis, Supervision, Writing – review & editing. **Ryan Bogdan:** Data curation, Supervision, Writing – review & editing. **Sridhar Kandala:** Data curation, Software, Supervision, Writing – review & editing. **Shelly Cooper:** Methodology, Supervision, Writing – review & editing. **Deanna M. Barch:** Data curation, Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare no conflicts of interest

Data availability

The ABCD dataset is openly available through the NIH Data Archive https://nda.nih.gov/abcd. The HCP young adult dataset was obtained from the open-access HCP young adult sample http://www.humanconnectome.org/..

Appendix A. Supplementary data

Supplementary material related to this article can be found online at https://doi.org/10.1016/j.neuroimage.2023.120471.

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