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Anatomical and functional correlates of human hippocampal volume asymmetry

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Abstract

Hemispheric asymmetry of the human hippocampus is well established, but poorly understood. We studied 110 healthy subjects with 3-Tesla MRI to explore the anatomical and functional correlates of the R>L volume asymmetry. We found that the asymmetry is limited to the anterior hippocampus (hemisphere $\times$ region interaction: $F(1,109) = 42.6$, $p < .001$). Anterior hippocampal volume was correlated strongly with the volumes of all four cortical lobes. In contrast, posterior hippocampal volume was correlated strongly only with occipital lobe volume, moderately with the parietal and temporal lobe volumes and not with the frontal lobe volume. The degree of R>L anterior hippocampal volume asymmetry predicted performance on a measure of basic cognitive abilities.

This provides evidence for regional specificity and functional implications of the well-known hemispheric asymmetry of hippocampal volume. We suggest that the developmental profile, genetic mechanisms and functional implications of R>L anterior hippocampal volume asymmetry in the human brain deserve further study.

Keywords

hippocampus; asymmetry; cognition; magnetic resonance imaging

Introduction

The structure of the human brain shows several hemispheric asymmetries (Geschwind and Galaburda, 1985; Toga and Thompson, 2003). Prominent examples include the frontal cortex (R>L), occipital cortex (L>R) and planum temporale (L>R) (Foundas et al., 1995; LeMay, 1976; Steinmetz, 1996). These structural asymmetries have long been interpreted as a correlate of hemispheric specialization in the service of optimal information processing (Toga and Thompson, 2003; Warrier et al., 2009). Furthermore, deviations from the normal pattern of asymmetry provide clues about underlying brain pathology (Csernansky et al., 2000; Wang et al., 2001) and can facilitate the understanding of pathophysiological processes in clinical populations (Barber et al., 2001). For example, investigators have proposed that abnormal asymmetry may serve as a neuroanatomical endophenotype (Qiu et al., 2009), risk factor (Oertel et al., 2010), or marker of genetic liability (Sharma et al., 1999) in schizophrenia.

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The hippocampus is among the regions in the human brain with known volume asymmetry (Pedraza et al., 2004; Shi et al., 2009). As the spatial resolution of MR imaging has improved, researchers have begun to explore the R>L volume asymmetry (Cook et al., 1992; Pegues et al., 2003; Sullivan et al., 2005; Thoma et al., 2009; Weiss et al., 2005), but the anatomical details and implications for our understanding of hippocampal function remain poorly understood.

The hippocampus plays a critical role in the formation of declarative and relational memory (Eichenbaum, 2004) and has been studied extensively in aging (Raz et al., 2004a; Raz et al., 2004b), Alzheimer's disease (Reitz et al., 2009; Sperling, 2007), temporal lobe epilepsy (Mechanic-Hamilton et al., 2009), and neuropsychiatric disorders such as schizophrenia (Heckers and Konradi, 2010). Many studies have explored the relationship of hippocampal volume and cognition (for review see (Van Petten, 2004)). For example, hippocampal volume predicts memory recall performance in an aging population (Reitz et al., 2009) and contextual fear conditioning in healthy subjects (Pohlack et al., 2011). A longitudinal study found that a decline in hippocampal volume preceded a specific decline in delayed word recall in elderly subjects (den Heijer et al., 2010). Most of these studies report only total hippocampal volumes and do not examine sub-regional effects. However, emerging evidence points towards a relationship between hippocampal asymmetry and individual measures of cognition (Wolf et al., 2001).

Here, we examined the R>L volume asymmetry of the hippocampus in healthy subjects. We also assessed the relationships of hippocampal and lobar volumes in each hemisphere. Finally, we investigated the relationship between hippocampal asymmetry and individual differences in cognition.

Materials and Methods

Subjects

We recruited 110 healthy subjects (54 females, 56 males) who provided informed consent in a manner approved by the Vanderbilt University Institutional Review Board. Subjects were recruited from the local community and were paid for their participation. All subjects underwent a Structured Clinical Interview for DSM-IV AXIS I Disorders (SCID) and were found to have no major medical and neurological illness, AXIS I psychiatric disorder or psychotropic medication use, including alcohol or substance abuse or dependence within three months prior to study enrollment. See Table 1 for subject demographic information.

MR image acquisition and preprocessing

All imaging data was collected on a 3T Philips Intera Achieva scanner located at the Vanderbilt University Institute of Imaging Science (VUIIS). A high-resolution T1-weighted fast field echo (FFE) structural scan (170 sagittal slices, matrix=256×256, 1.0 mm isovoxel resolution, TR/TE=8.0/3.7 ms) was acquired as part of a larger imaging protocol. Foam padding was used to stabilize the head. Earplugs and headphones were given to the subject to minimize scanner noise. Fiducial markers (vitamin E capsules) were placed on the subject's right forehead for reference.

Volumetric analysis of the hippocampus

Volumetric analysis was completed by a single rater (AW) using a previously established hippocampal segmentation protocol described in detail elsewhere (Pruessner et al., 2000). All manual segmentations were completed using 3DSlicer (version 3.4), a free software package used for visualization and medical image computing (Pieper, 2004). 3DSlicer

allows for simultaneous viewing in three orientations (coronal, sagittal, and horizontal) and automatically calculates the volumes of manually segmented structures.

The hippocampal segmentation method was standardized across all subjects. First, the right hippocampus was segmented in 1mm slice intervals in the sagittal orientation, starting with the most lateral section and proceeding medially until the hippocampus was no longer visible. This method was repeated for the left hippocampus. Next, the sagittal outline was further refined using the Pruessner protocol in the coronal orientation, starting with the most posterior section and proceeding anteriorly until the hippocampus recedes under the amygdala (see supplemental material for further details of the segmentation protocol).

Both hippocampi were then divided into anterior (uncus) and posterior (body and tail) regions. The uncus is defined as the anterior portion of the hippocampus that undergoes a folding over and rotation in a hook-like fashion (uncus is Latin for hook) during brain development (Gloor, 1997). It can be identified in coronal sections by the presence of more than one cut through the hippocampus (Duvernoy, 1998) and a protrusion of hippocampal tissue medially into the quadrigeminal cistern towards the crus cerebri (Figure 1A). This anterior-posterior demarcation was verified in the sagittal orientation (Figure 1C). This method resulted in four separate regions of interest (ROIs): Right Anterior (RA), Right Posterior (RP), Left Anterior (LA), and Left Posterior (LP). Reliability statistics were computed by blindly segmenting 16 randomly selected images at two different time points to determine Intraclass Correlation Coefficients (ICC). This resulted in the following ICC values: 0.95 left, 0.98 left anterior, 0.88 left posterior, 0.95 right, 0.96 right anterior, and 0.89 right posterior hippocampus.

Lobar Volume Analysis

Lobar volumes were calculated using a FreeSurfer (<http://surfer.nmr.mgh.harvard.edu>) segmentation procedure described in detail elsewhere (Fischl et al., 2002).

SCIP Analysis

We used the Screen for Cognitive Impairment in Psychiatry (SCIP) to collect data on 86 of the 110 healthy subjects. The SCIP is a measurement designed to quantify basic cognitive abilities (Purdon, 2005). The SCIP contains five sub-tests which measure different cognitive processes: Verbal Learning Test-Immediate (VLT-I); Working Memory Test (WMT); Verbal Fluency Test (VFT); Verbal Learning Test-Delayed (VLT-D); and Processing Speed Test (PST). The group averages for the different tests are presented in Table 3. All test averages are within the normal range of a sample population assessed by Purdon, 2005 (n = 185, 1st year college sample, IQ approx. 110).

Statistical Analysis

All data were analyzed using Predictive Analytics Software (PASW) Statistics 18. We used repeated measures analysis of variance (ANOVA) to test for main effects of hemisphere (left/right) and region (anterior/posterior) and a possible interaction on hippocampal volumes. We corrected raw hippocampal volumes using the following correction formula (Jack et al., 1989): $\text{Volume}_i(\text{adjusted}) = \text{volume}_i(\text{observed}) - B(\text{CM}_i - \text{CM}_{\text{mean}})$, where CM_i = the subject's cerebral measure, CM_{mean} = group average of the cerebral measure, and B is the slope of the regression line of the hippocampal region, regressed on the cerebral measure. We assessed hemispheric hippocampal asymmetry (total, anterior, and posterior) with the Asymmetry Index (AI) formula: $\text{AI} = ((R-L)/0.5*(R+L))$, which corrects for overall hippocampal volume (Galaburda, 1987). We used bivariate correlations to relate SCIP measurements to hippocampal volume and individual asymmetry indices (AIs). Correlations with SCIP sub-test scores were considered significant if $p < 0.05/5$.

Within the sample we recruited 86 participants under a protocol requiring the Wechsler Test of Adult Reading (WTAR) as a measure of IQ, and 24 participants under a protocol utilizing the North American Adult Reading Test (NART). This latter group was not administered the SCIP and therefore did not contribute data to the correlation analysis of cognitive function and hippocampal volume. All main findings of the study remained unchanged after removal of the 13 left-handed subjects. All correlation analyses remained unchanged with gender added as a covariate.

Results

Hippocampal Volume

Total hippocampal volume was larger in the right hemisphere (main effect of hemisphere: $F(1,109) = 62.7, p < .001$) (Figure 2A). Our separation into anterior and posterior volumes resulted in significantly larger anterior hippocampal volumes (main effect of region: $F(1,109) = 12.7, p = .001$). Crucially, we found a hemisphere $\times$ region interaction ($F(1,109) = 42.6, p < .001$), due to larger right $>$ left anterior volumes ($t(109) = 8.7, p < 0.001$) and no hemispheric difference of posterior hippocampal volumes ($t(109) = -0.79, p = .43, ns$) (Figure 2 and Table 2). To further illustrate this hemisphere $\times$ region interaction, we plotted out the Asymmetry Index ($AI = ((R-L)/0.5*(R+L))$) for total, anterior, and posterior hippocampal volumes (Figure 2B). This revealed a remarkably consistent R $>$ L asymmetry of anterior (89 out of 110 cases) but not posterior (48 out of 110 cases) hippocampal volumes (Figure 2B). To rule out the possibility that the hemispheric asymmetry of anterior hippocampal volume was part and parcel of a larger hemispheric asymmetry of lobar or cortical volumes, we replicated the same hemisphere $\times$ region interaction of larger right $>$ left anterior hippocampal volumes with hippocampal volumes that were a) corrected for hemispheric volume (Jack et al., 1989) ($F(1,109) = 41.2, p < .001$) or b) normalized using the T1 template in SPM8 into MNI space ($F(1,109) = 39.4, p < .001$).

Correlations with lobar volumes

We found a gradient of hippocampal-lobar volume correlations for the posterior hippocampus: occipital lobe volume was strongly correlated, parietal and temporal lobe volumes were moderately correlated, but frontal lobe volumes were not correlated (Figure 4). In contrast, there was no gradient of hippocampal-lobar volume correlations for anterior hippocampal volume, as it was equally and strongly correlated with the volumes of all four lobes (all r values $> .42, p < .001$) (Figure 4).

Correlations with cognitive function

Overall SCIP performance correlated with the asymmetry index of the whole hippocampus ($r = .38, p < .001$) (Figure 4A). This relationship was due to the anterior region ($r = .40, p < .001$), not the posterior region ($r = -.06, p = .61$; Figures 4B and 4C). To further characterize this association, we correlated the individual, average Z-scores from each sub-test of the SCIP with hippocampal asymmetry. This analysis revealed significant correlations between the anterior AI and immediate verbal learning (VLT-I; $r = .37, p < .001$) and verbal fluency (VFT; $r = .31, p = .004$). In contrast, we found no significant correlations between posterior hippocampal AI and any SCIP sub-test average Z-score (all r values $< .07; p > .53$), except for the immediate verbal learning test which was trending at $r = -.21, p = .055$.

Overall SCIP performance was also correlated with the raw volume of the right anterior hippocampal region ($r = .22, p = .045$), but not with the other three regions (all r values $< .071, p$ values > 0.51).

Since we had not collected SCIP data in all subjects, we confirmed that the subset with SCIP data and the total sample did not differ with regard to the asymmetry indices (total: $F(1,108) = 1.02$, $p = .32$; anterior: $F(1,108) = .33$, $p = .57$; posterior: $F(108) = .66$, $p = .42$) and hippocampal volume (main effect of group: $F(1,109) = 2.68$, $p = .104$), supporting the notion that the correlations we found would be similar in the larger sample.

Discussion

We confirmed the well-known R>L hemispheric asymmetry of hippocampal volume. Our study of a large sample of healthy subjects adds three new findings. First, we show that this asymmetry is limited to the anterior hippocampus. Second, we show that anterior hippocampal volumes are strongly correlated with the volumes of all four cortical lobes, whereas the posterior hippocampus has a distinct posterior > anterior gradient. Third, we show that the R>L hemispheric asymmetry of the anterior, but not the posterior, hippocampus is correlated with a measure of general cognitive function. These findings indicate hemispheric and regional differences in the development of the hippocampus, resulting in distinct patterns of anatomical connectivity and cognitive function.

The R>L hemispheric asymmetry of hippocampal volume is a subtle, yet robust finding (Pedraza et al., 2004; Shi et al., 2009). Our finding that the hemispheric asymmetry is limited to the anterior hippocampus adds to the emerging literature of an anterior-posterior segregation of hippocampal anatomy and function (Moser and Moser, 1998). Anterior-posterior gradients have now been documented for hippocampal connectivity (Soderlund et al., 2011), gene expression (Fanselow and Dong, 2010), activation patterns (Milton et al., 2011) and volume changes during aging (Rajah et al., 2010).

The hemisphere $\times$ region interaction of hippocampal volume fits into the neurodevelopmental model of a growth vector that proceeds from the right anterior to the left posterior region of the hemispheres (Best, 1988). The most prominent sign of this vector are right frontal petalia, i.e. impressions left on the inner surface of the skull by protrusions of the right frontal cortex (Toga and Thompson, 2003). We interpret our finding of right anterior > left anterior hippocampal volume as a result of this growth vector. The right > left hippocampal volume ratio tends to decrease during development (Giedd et al., 1996; Gogtay et al., 2006; Szabo et al., 1999). Abnormal increases of right > left hippocampal asymmetry have been linked to the emergence of complex febrile seizures in children (Szabo et al., 1999) and psychopathy in adults (Raine et al., 2004). The mechanisms of the right > left hippocampal asymmetry are not known and may include genetic as well as environmental factors (Tang et al., 2008; Verstynen et al., 2001). The anatomical details of the R>L hippocampal asymmetry are complex and involve rotations and a folding over of the most anterior portions back onto the hippocampus during development, creating the uncus (Gloor, 1997). This “folding over” provides the basis for our demarcation of the hippocampus into anterior and posterior regions. The uncus is particularly prominent in the human brain (see figure 2–38 in (Gloor, 1997)) and is the most highly developed part of the hippocampus in primates. We show here that the volume of the uncus is strongly correlated with the volume of all four lobes of the cerebral hemisphere. In contrast, for the posterior hippocampus we find a posterior > anterior gradient, indicating a stronger relationship with the occipital cortex (Kaas, 2008).

Our data contribute to the growing literature on a functional differentiation across the long axis of the hippocampus (Bast, 2007; Fanselow and Dong, 2010; Moser and Moser, 1998). We conducted an exploratory analysis, correlating regional hippocampal volumes with the performance on the Screen for Cognitive Impairment in Psychiatry (SCIP) (Purdon, 2005). We found a relationship between the right anterior region and overall SCIP performance and

between the degree of R>L asymmetry and performance on the SCIP, specifically the subtests for verbal learning, verbal fluency, and motor-processing speed. While these findings are preliminary, they are supported by other reports of a critical role of the anterior hippocampus in memory encoding and retrieval (Small et al., 2001), particularly in relational/associative memory (Addis and Schacter, 2008; Chua et al., 2007; Giovanello et al., 2009; Giovanello et al., 2004). The recent study by Rajah et al. is particularly relevant here: they reported a relationship between anterior hippocampal volumes and context retrieval performance in young adults (Rajah et al., 2010). It is not clear at this point how the hemispheric asymmetry of anterior hippocampal volumes translates into cognitive benefits. If confirmed, it will be important to explore the structural and functional correlates of anterior hippocampal connectivity.

Our study has several limitations. First, we used a landmark that was visible on coronal MR images to define the anterior/posterior regions of the hippocampus. While it would have been ideal to use a histological marker (akin to the anatomical criteria for the hippocampal sectors CA 1 – CA 4), this is not feasible in human neuroimaging data. We believe that our definition of the anterior region (uncus) based on an intrinsic hippocampal marker is superior to segmentation protocols that have used markers outside the hippocampus (e.g., lateral ventricle or lateral geniculate body) and is similar to previous studies (Malykhin et al., 2007; Weiss et al., 2005). Second, intra-rater reliability was less accurate in the posterior hippocampus, due to the less distinct boundaries of the hippocampal tail. However, this is very similar to other studies (Malykhin et al., 2007; Rajah et al., 2010) and is within the accepted range for hippocampal volume studies (ICC $\geq$ 0.85; (Jeukens et al., 2009)). Third, SCIP data were collected only on a subset of subjects (86 of the 110 healthy subjects). However, comparisons between the subjects with and without SCIP data revealed no between group differences in hippocampal volume or asymmetry and thus our findings are likely to be representative of the entire cohort.

In summary, we found that the asymmetry of hippocampal volume is specific to the uncus. It's unique developmental profile makes this region an intriguing target for further studies of mechanism and function of the human hippocampus.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

- Addis DR, Schacter DL. Constructive episodic simulation: temporal distance and detail of past and future events modulate hippocampal engagement. *Hippocampus*. 2008; 18(2):227–37. [PubMed: 18157862]
- Barber R, McKeith IG, Ballard C, Gholkar A, O'Brien JT. A comparison of medial and lateral temporal lobe atrophy in dementia with Lewy bodies and Alzheimer's disease: magnetic resonance imaging volumetric study. *Dement Geriatr Cogn Disord*. 2001; 12(3):198–205. [PubMed: 11244213]
- Bast T. Toward an integrative perspective on hippocampal function: from the rapid encoding of experience to adaptive behavior. *Reviews in the neurosciences*. 2007; 18(3–4):253–81. [PubMed: 18019609]
- Best, CT. The emergence of cerebral asymmetries in early human development: A literature review and a neuroembryological model. In: Moltese, DL.; Segalowitz, SJ., editors. *Brain lateralization in children: Developmental implications*. New York: Guilford Press; 1988. p. 5-34.
- Chua EF, Schacter DL, Rand-Giovannetti E, Sperling RA. Evidence for a specific role of the anterior hippocampal region in successful associative encoding. *Hippocampus*. 2007; 17(11):1071–80. [PubMed: 17604351]

- Cook MJ, Fish DR, Shorvon SD, Straughan K, Stevens JM. Hippocampal volumetric and morphometric studies in frontal and temporal lobe epilepsy. *Brain*. 1992; 115(4):1001–1015. [PubMed: 1393499]
- Csernansky JG, Wang L, Joshi S, Miller JP, Gado M, Kido D, McKeel D, Morris JC, Miller MI. Early DAT is distinguished from aging by high-dimensional mapping of the hippocampus. *Dementia of the Alzheimer type*. *Neurology*. 2000; 55(11):1636–43. [PubMed: 11113216]
- den Heijer T, van der Lijn F, Koudstaal PJ, Hofman A, van der Lugt A, Krestin GP, Niessen WJ, Breteler MM. A 10-year follow-up of hippocampal volume on magnetic resonance imaging in early dementia and cognitive decline. *Brain*. 2010; 133(Pt 4):1163–72. [PubMed: 20375138]
- Duvernoy, HM. *The human hippocampus*. Berlin: Springer Verlag; 1998.
- Eichenbaum H. Hippocampus: cognitive processes and neural representations that underlie declarative memory. *Neuron*. 2004; 44(1):109–20. [PubMed: 15450164]
- Fanselow MS, Dong HW. Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron*. 2010; 65(1):7–19. [PubMed: 20152109]
- Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002; 33(3):341–55. [PubMed: 11832223]
- Foundas AL, Leonard CM, Heilman KM. Morphologic cerebral asymmetries and handedness. The pars triangularis and planum temporale. *Arch Neurol*. 1995; 52(5):501–8. [PubMed: 7733846]
- Galaburda AM, Corsiglia J, Rosen G, Sherman GF. Planum Temporale asymmetry, reappraisal since Geschwind and Levitsky. *Neuropsychologia*. 1987; 25:853–868.
- Geschwind N, Galaburda AM. Cerebral lateralization. Biological mechanisms, associations, and pathology: I. A hypothesis and a program for research. *Archives of neurology*. 1985; 42(5):428–59. [PubMed: 3994562]
- Giedd JN, Snell JW, Lange N, Rajapakse JC, Casey BJ, Kozuch PL, Vaituzis AC, Vauss YC, Hamburger SD, Kaysen D, et al. Quantitative magnetic resonance imaging of human brain development: ages 4–18. *Cerebral cortex*. 1996; 6(4):551–60. [PubMed: 8670681]
- Giovanello KS, Schnyer D, Verfaellie M. Distinct hippocampal regions make unique contributions to relational memory. *Hippocampus*. 2009; 19(2):111–7. [PubMed: 18727049]
- Giovanello KS, Schnyer DM, Verfaellie M. A critical role for the anterior hippocampus in relational memory: evidence from an fMRI study comparing associative and item recognition. *Hippocampus*. 2004; 14(1):5–8. [PubMed: 15058477]
- Gloor, P. *The Temporal Lobe and Limbic System*. Oxford: Oxford University Press; 1997.
- Gogtay N, Nugent TF 3rd, Herman DH, Ordóñez A, Greenstein D, Hayashi KM, Clasen L, Toga AW, Giedd JN, Rapoport JL, et al. Dynamic mapping of normal human hippocampal development. *Hippocampus*. 2006; 16(8):664–72. [PubMed: 16826559]
- Heckers, S.; Konradi, C. Hippocampal pathology in schizophrenia. In: Swerdlow, NR., editor. *Current Topics in Behavioral Neurosciences: Behavioral Neurobiology of Schizophrenia and Its Treatment*. New York: Springer; 2010. in press
- Jack CR Jr, Twomey CK, Zinsmeister AR, Sharbrough FW, Petersen RC, Cascino GD. Anterior temporal lobes and hippocampal formations: normative volumetric measurements from MR images in young adults. *Radiology*. 1989; 172(2):549–54. [PubMed: 2748838]
- Jeukens CR, Vlooswijk MC, Majoie HJ, de Krom MC, Aldenkamp AP, Hofman PA, Jansen JF, Backes WH. Hippocampal MRI volumetry at 3 Tesla: reliability and practical guidance. *Invest Radiol*. 2009; 44(9):509–17. [PubMed: 19692839]
- Kaas JH. The evolution of the complex sensory and motor systems of the human brain. *Brain Res Bull*. 2008; 75(2–4):384–90. [PubMed: 18331903]
- LeMay M. Morphological cerebral asymmetries of modern man, fossil man, and nonhuman primate. *Ann N Y Acad Sci*. 1976; 280:349–66. [PubMed: 827951]
- Malykhin NV, Bouchard TP, Ogilvie CJ, Coupland NJ, Seres P, Camicioli R. Three-dimensional volumetric analysis and reconstruction of amygdala and hippocampal head, body and tail. *Psychiatry Research*. 2007; 155(2):155–65. [PubMed: 17493789]

- Mechanic-Hamilton D, Korczykowski M, Yushkevich PA, Lawler K, Pluta J, Glynn S, Tracy JJ, Wolf RL, Sperling MR, French JA, et al. Hippocampal volumetry and functional MRI of memory in temporal lobe epilepsy. *Epilepsy Behav.* 2009; 16(1):128–38. [PubMed: 19674939]
- Milton F, Muhler N, Butler CR, Benattayallah A, Zeman AZ. The neural correlates of everyday recognition memory. *Brain Cogn.* 2011
- Moser MB, Moser EI. Functional differentiation in the hippocampus. *Hippocampus.* 1998; 8(6):608–19. [PubMed: 9882018]
- Oertel V, Knochel C, Rotarska-Jagiela A, Schonmeyer R, Lindner M, van de Ven V, Haenschel C, Uhlhaas P, Maurer K, Linden DE. Reduced laterality as a trait marker of schizophrenia—evidence from structural and functional neuroimaging. *J Neurosci.* 2010; 30(6):2289–99. [PubMed: 20147555]
- Pedraza O, Bowers D, Gilmore R. Asymmetry of the hippocampus and amygdala in MRI volumetric measurements of normal adults. *J Int Neuropsychol Soc.* 2004; 10(5):664–78. [PubMed: 15327714]
- Pegues MP, Rogers LJ, Amend D, Vinogradov S, Deicken RF. Anterior hippocampal volume reduction in male patients with schizophrenia. *Schizophr Res.* 2003; 60(2–3):105–15. [PubMed: 12591575]
- Pieper, S.; Halle, M.; Kikinis, R. Proceedings of the 1st IEEE International Symposium on Biomedical Imaging: From Nano to Macro; 2004. p. 632–635.
- Pohlack ST, Nees F, Liebscher C, Cacciaglia R, Diener SJ, Ridder S, Woermann FG, Flor H. Hippocampal but not amygdalar volume affects contextual fear conditioning in humans. *Hum Brain Mapp.* 2011
- Pruessner JC, Li LM, Serles W, Pruessner M, Collins DL, Kabani N, Lupien S, Evans AC. Volumetry of hippocampus and amygdala with high-resolution MRI and three-dimensional analysis software: minimizing the discrepancies between laboratories. *Cereb Cortex.* 2000; 10(4):433–42. [PubMed: 10769253]
- Purdon, SE. The Screen for Cognitive Impairment in Psychiatry (SCIP): Administration Manual and Normative Data. Edmonton, Alberta: PNL Inc; 2005.
- Qiu A, Wang L, Younes L, Harms MP, Ratnanather JT, Miller MI, Csernansky JG. Neuroanatomical asymmetry patterns in individuals with schizophrenia and their non-psychotic siblings. *Neuroimage.* 2009; 47(4):1221–9. [PubMed: 19481156]
- Raine A, Ishikawa SS, Arce E, Lencz T, Knuth KH, Bihle S, LaCasse L, Colletti P. Hippocampal structural asymmetry in unsuccessful psychopaths. *Biological psychiatry.* 2004; 55(2):185–91. [PubMed: 14732599]
- Rajah MN, Kromas M, Han JE, Pruessner JC. Group differences in anterior hippocampal volume and in the retrieval of spatial and temporal context memory in healthy young versus older adults. *Neuropsychologia.* 2010; 48(14):4020–30. [PubMed: 20946907]
- Raz N, Gunning-Dixon F, Head D, Rodrigue KM, Williamson A, Acker JD. Aging, sexual dimorphism, and hemispheric asymmetry of the cerebral cortex: replicability of regional difference in volume. *Neurobiology of Aging.* 2004a; 25(3):377–396. [PubMed: 15123343]
- Raz N, Rodrigue KM, Head D, Kennedy KM, Acker JD. Differential aging of the medial temporal lobe: A study of a five-year change. *Neurology.* 2004b; 62(3):433–438. [PubMed: 14872026]
- Reitz C, Brickman AM, Brown TR, Manly J, DeCarli C, Small SA, Mayeux R. Linking hippocampal structure and function to memory performance in an aging population. *Arch Neurol.* 2009; 66(11):1385–92. [PubMed: 19901171]
- Sharma T, Lancaster E, Sigmundsson T, Lewis S, Takei N, Gurling H, Barta P, Pearson G, Murray R. Lack of normal pattern of cerebral asymmetry in familial schizophrenic patients and their relatives—The Maudsley Family Study. *Schizophr Res.* 1999; 40(2):111–20. [PubMed: 10593451]
- Shi F, Liu B, Zhou Y, Yu C, Jiang T. Hippocampal volume and asymmetry in mild cognitive impairment and Alzheimer's disease: Meta-analyses of MRI studies. *Hippocampus.* 2009; 19(11):1055–64. [PubMed: 19309039]
- Small SA, Nava AS, Perera GM, DeLaPaz R, Mayeux R, Stern Y. Circuit mechanisms underlying memory encoding and retrieval in the long axis of the hippocampal formation. *Nature neuroscience.* 2001; 4(4):442–9.

- Soderlund H, Moscovitch M, Kumar N, Mandic M, Levine B. As time goes by: Hippocampal connectivity changes with remoteness of autobiographical memory retrieval. *Hippocampus*. 2011
- Sperling R. Functional MRI studies of associative encoding in normal aging, mild cognitive impairment, and Alzheimer's disease. *Ann N Y Acad Sci*. 2007; 1097:146–55. [PubMed: 17413017]
- Steinmetz H. Structure, functional and cerebral asymmetry: in vivo morphometry of the planum temporale. *Neurosci Biobehav Rev*. 1996; 20(4):587–91. [PubMed: 8994197]
- Sullivan EV, Marsh L, Pfefferbaum A. Preservation of hippocampal volume throughout adulthood in healthy men and women. *Neurobiology of Aging*. 2005; 26(7):1093–1098. [PubMed: 15748789]
- Szabo CA, Wyllie E, Siavalas EL, Najm I, Ruggieri P, Kotagal P, Luders H. Hippocampal volumetry in children 6 years or younger: assessment of children with and without complex febrile seizures. *Epilepsy research*. 1999; 33(1):1–9. [PubMed: 10022361]
- Tang AC, Zou B, Reeb BC, Connor JA. An epigenetic induction of a right-shift in hippocampal asymmetry: selectivity for short- and long-term potentiation but not post-tetanic potentiation. *Hippocampus*. 2008; 18(1):5–10. [PubMed: 17924531]
- Thoma RJ, Monnig M, Hanlon FM, Miller GA, Petropoulos H, Mayer AR, Yeo R, Euler M, Lysne P, Moses SN, et al. Hippocampus volume and episodic memory in schizophrenia. *J Int Neuropsychol Soc*. 2009; 15(2):182–95. [PubMed: 19203430]
- Toga AW, Thompson PM. Mapping brain asymmetry. *Nat Rev Neurosci*. 2003; 4(1):37–48. [PubMed: 12511860]
- Van Petten C. Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. *Neuropsychologia*. 2004; 42(10):1394–1413. [PubMed: 15193947]
- Verstynen T, Tierney R, Urbanski T, Tang A. Neonatal novelty exposure modulates hippocampal volumetric asymmetry in the rat. *Neuroreport*. 2001; 12(14):3019–22. [PubMed: 11568629]
- Wang L, Joshi SC, Miller MI, Csernansky JG. Statistical analysis of hippocampal asymmetry in schizophrenia. *Neuroimage*. 2001; 14(3):531–45. [PubMed: 11506528]
- Warrier C, Wong P, Penhune V, Zatorre R, Parrish T, Abrams D, Kraus N. Relating structure to function: Heschl's gyrus and acoustic processing. *J Neurosci*. 2009; 29(1):61–9. [PubMed: 19129385]
- Weiss AP, Dewitt I, Goff D, Ditman T, Heckers S. Anterior and posterior hippocampal volumes in schizophrenia. *Schizophr Res*. 2005; 73(1):103–12. [PubMed: 15567082]
- Wolf H, Grunwald M, Kruggel F, Riedel-Heller SG, Angerhofer S, Hojjatoleslami A, Hensel A, Arendt T, Gertz H. Hippocampal volume discriminates between normal cognition; questionable and mild dementia in the elderly. *Neurobiol Aging*. 2001; 22(2):177–86. [PubMed: 11182467]

Figure 1. Example of the anterior-posterior demarcation showing A) the last anterior section, B) the first posterior section, C) a sagittal section of the right hippocampus, and D) a bird's eye view of a the subject's 3D rendering showing both right (blue) and left (red) hippocampi.

Figure 2.

A) Raw hippocampal volumes showing volume differences of the anterior (right>left) but not posterior regions. B) Individual Asymmetry Indices ($AI = (R - L) / 0.5(R + L)$) for total, anterior, and posterior hippocampal regions showing a systematic R>L hemispheric asymmetry (indicated by the blue upward-facing bars) that is driven by the asymmetry of the anterior region. Subjects are ordered by Total AI.

Figure 3. Correlations between A) total anterior (R+L) and B) total posterior (R+L) hippocampal volumes and total lobar (R+L) volumes (i.e., frontal, parietal, temporal, and occipital). Dark grey = $p < .001$, light grey = $p < .02$. Correlation (r) values are indicated in each lobar region.

Figure 4. Correlations between the individual average Z-scores and A) total, B) anterior, and C) posterior Asymmetry Indices (AI) showing a relationship between total hippocampal asymmetry (R>L) and cognitive performance. This relationship is driven by the asymmetries (R>L) of the anterior hippocampus.

Table 1

Demographic Information

Age *	32.3 ± 10.7
Gender	M: 56, F: 54
Years of Education *	15.3 ± 2.3
Estimated IQ (WTAR; n=86) **	109.2 ± 2.3
Estimated IQ (NART; n=24) **	115.3 ± 5.8
Handedness	R: 97, L: 10, Amb:3
Race	W: 83, B: 24, O: 3

* Values are mean ± SD

** The Wechsler Test of Adult Reading (WTAR) was used for estimated Full Scale IQ on 86 of the 110 subjects. For the remaining 24 subjects, the National Adult Reading Test (NART) was used.

R = Right; L = Left; Amb = Ambidextrous; W = White; B = Black; O = Other

Table 2

Hippocampal Volumes

Region	Raw (mm ³)		Normalized (mm ³)	
	Left	Right	Left	Right
Total	3352 ± 358	3504 ± 384	4850 ± 528	5055 ± 609
Anterior	1683 ± 288	1846 ± 284	2425 ± 371	2644 ± 402
Posterior	1669 ± 196	1658 ± 206	2424 ± 343	2411 ± 351

Volumes (means ± SD) for total, anterior, and posterior hippocampal regions.

Table 3

SCIP Data

Test	Group Scores	Average Z-score
VLT-I	23.92 ± 2.78	0.11
WMT	20.79 ± 2.49	0.05
VFT	18.47 ± 4.47	0.22
VLT-D	7.28 ± 1.79	-0.20
PST	13.06 ± 2.86	-0.60
	Overall AVG Z Score	-0.08

Subtest group scores (mean ± SD) for the Screen for Cognitive Impairment in Psychiatry (SCIP) in 86 subjects out of our total sample of 110 subjects. The subtests are: Verbal Learning Test-Immediate (VLT-I), Working Memory Test (WMT), Verbal Fluency Test (VFT), Verbal Learning Test-Delayed (VLT-D), and Processing Speed Test (PST). Group averages of the raw scores and average z-scores (derived from the original Purdon 2005 control sample) are listed.