Published in final edited form as:

Neuropsychologia. 2007 September 20; 45(12): 2874–2881. doi:10.1016/j.neuropsychologia.2007.05.009.

Human experience seeking correlates with hippocampus volume: convergent evidence from manual tracing and voxel-based morphometry

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Abstract

Experience-seekers continuously pursue novel environmental stimuli, a tendency linked to genetic variation in mesolimbic dopamine transmission. However, the neuroanatomical basis accompanying these genetic and neurochemical associations is unknown. Animal and human experimental results suggest a central role for the hippocampus in processing novel stimuli. Here, we explored whether differences in human experience seeking are related to variations in hippocampal volume. High resolution anatomic MR images were analyzed in 40 individuals who ranged from low through high on a validated experience seeking personality scale. Manual tracing analysis demonstrated positive correlation between right hippocampal volumes and scores on the experience seeking scale. A separate voxel-based morphometric analysis confirmed these results and localized the significant increase to the anterior portion of right hippocampal grey matter. We tested and were able to reject the possibility that results were mediated by a personality trait related to, but distinct from, experience seeking. The present data provide the first direct evidence for a relationship between human experience seeking and brain structure. In addition, these results provide new ecologically relevant evidence for a link between right anterior hippocampus and novelty processing.

Introduction

Why do some people perpetually seek novelty while other people prefer what is familiar? Experience seeking, a tendency to be attracted to environments and stimuli that are novel, has been identified as one dimension of the multidimensional sensation seeking personality trait (Zuckerman et al., 1978). Experience seekers have been characterized as those with a high need for mental stimulation related to the pursuit of unfamiliar and complex environmental stimuli (Zuckerman et al., 1978). At the behavioral level, experience seekers tend to engage in

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investigatory behaviors such as exploring unknown locations, trying new foods and seeking interaction with individuals from different backgrounds. By contrast, individuals who are low in the experience seeking trait tend to be more conservative in their choices, preferring well-known environments and people (Zuckerman, 1994).

Genetic studies have demonstrated an association between human experience seeking behavior and genetic variation in dopamine (DA) transmission. At least two DA-related genes have been implicated: the D4 dopamine receptor gene (DRD4; Benjamin et al., 1996; Ebstein et al., 1996) and catechol-O-methyltransferase (COMT; Reuter and Hennig, 2005). A significant association between experience seeking and seven-repeat allele (a long form) of the 16-amino-acid polymorphism of the DRD4 gene has been reported (Benjamin et al., 1996; Ebstein et al., 1996). In addition, experience seeking scores were reported to be higher in a group of subjects with the val/met genotype of the COMT gene (Reuter and Hennig, 2005).

It remains unknown whether experience seeking has a neuroanatomical basis that accompanies its genetic and neurochemical bases. Data from the rodent literature have demonstrated a central role for the hippocampus in DA transmission related to processing novel stimuli. The hippocampus has been shown to be critical in assessing whether a stimulus/environment is novel (Legault and Wise, 2001) and in the subsequent regulation of novelty-dependent dopaminergic activity (Legault and Wise, 2001; Lemon and Manahan-Vaughan, 2006). Similarly, direct hippocampal stimulation increases exploratory behavior in rodents (Flicker and Geyer, 1982; Yang and Mogenson, 1987). Finally, rodent models suggest that the hippocampus is capable of comparing incoming information with stored memories in order to index whether that information is novel (Lisman and Grace, 2005).

The human hippocampus is also known to play a role in indexing novelty. A hippocampal response during the processing of novel stimuli has been demonstrated using in vivo recordings (Fried et al., 1997), and event-related potentials (Knight, 1996). In addition, functional neuroimaging studies have demonstrated a prominent response in hippocampus during viewing of novel compared to familiar stimuli, and rapid habituation of this hippocampal response as stimuli become more familiar (Tulving et al., 1996; Yamaguchi et al., 2004; O'Kane et al., 2005).

Together, such data from controlled laboratory studies have indicated a role for the hippocampus in novelty processing. It remains unknown whether the hippocampus-novelty processing relationship tracks with naturally occurring individual differences in human behavior. If the relationship does extend into naturalistic behavioral settings then one possibility would be that structural variability in hippocampal volume may contribute to human individual differences in the tendency to pursue novelty.

In the present research, we explored this question by examining the relationship between experience seeking and hippocampus volume in a group of young adults who varied across the continuum of the experience seeking trait. Two analyses were performed. First, hippocampal volumes were traced manually using conventional boundary guidelines. Second, whole-brain voxel-based morphometry was performed to validate results from the manual tracing analysis and explore the possibility that experience seeking may correlate with volume of brain regions outside the hippocampus. Results demonstrate that individual differences in experience seeking behavior are associated with differences in grey matter volume in the right anterior hippocampus.

Materials and Methods

Participants

Participants were initially recruited as part of a separate functional magnetic resonance imaging (fMRI) study exploring brain activation patterns associated with the multidimensional personality trait of sensation seeking. Participants were recruited based on their responses to an online version of the Brief Sensation Seeking Scale (Hoyle et al., 2002). Twenty individuals scoring in the top quartile of population norms (high sensation seekers; 10 males) and twenty individual scoring in the bottom quartile (low sensation seekers; 10 males) were invited to participate in the fMRI study. Participant age ranged between 18 and 25 years (mean = 20.7, SD = 2.08) with a mean education of 14.23 years (S.D. = 1.72), and reported to not be recreational drug users or smokers. Upon visiting the laboratory, participants completed a battery of personality measures, including the form V Sensation Seeking Scale (SSS Form V; Zuckerman et al., 1978). All participants provided written informed consent in a manner approved by the University of Kentucky Institutional Review Board and were paid for participating.

Participants in the present experiment were the same forty young adult volunteers (20 men and 20 women) described above. The Brief Sensation Seeking Scale on which participants were recruited provides an overall assessment of the multidimensional sensation seeking personality trait, but does not enable assessment of individual, unidimensional sensation seeking personality traits assessed by the SSS Form V (Hoyle et al., 2002). Thus, despite being recruited on the basis of high or low scores on the Brief Sensation Seeking scale, participants' scores were normally distributed on the experience seeking subscale of SSS Form V (skewness = -.219; Kertosis = -.615). The normal distribution of participants' scores on the ES subscale made possible a correlation analysis to explore how individual differences in the tendency to pursue novelty are associated with hippocampal structure (using the anatomic brain scans collected as part of the fMRI study).

However, given that our subjects were originally selected (for inclusion in a larger study) based on having either high or low scores on the Brief Sensation Seeking Scale, as opposed to being selected randomly, it is relevant to consider how our subjects' scores on the ES subscale compare to scores on the ES subscale collected in the original normative study. The original ES subscale norms were collected in late 1980's on university students of similar age and education as our subjects. The means and standard deviations (SDs) on the ES subscale for males and females in the original norms were: Males, 5.2 (2.4); Females: 4.8 (2.1) (Zuckerman, 1994). The means and SDs on ES subscale for males and females in our sample were Males: 5.3 (2.3); Females: 5.2 (2.1). The fact that the standard deviation of our sample on the ES subscale was almost identical to that of the sample on which the scale was normed suggests that our participants' scores ranged across the ES dimension in a manner similar to those of other university students selected in a more random manner (selected independently from scores on the Brief Sensation Seeking Scale).

An observed relationship between experience seeking and hippocampal volume could reflect either an association between hippocampal volume and the tendency to pursue novelty or a more general tendency to pursue any form mental stimulation (e.g., any form of sensation seeking). Scores on two other sensation seeking subscales were also analyzed within the context of hippocampal volumes to address this issue. The two other subscales were thrill seeking and disinhibition. Like the experience seeking subscale, the thrill seeking and disinhibition subscales assess the need for intense mental stimulation. Importantly, however, unlike the experience seeking subscale, the other two subscales assess the tendency to pursue behavior that is physically dangerous (thrill seeking) or unrestrained (disinhibition), irrespective of whether these behaviors are novel or not (Zuckerman, 1994). In contrast, the experience

seeking scale assesses the tendency to pursue mental stimulation specifically related to environments and behaviors that are novel (Zuckerman, 1994). These three scales are described below.

Personality Scales

The three subscales described below are part of the form V Sensation Seeking Scale (SSS Form V; Zuckerman et al., 1978). Each subscale has 10 forced-choice items in which participants are asked to choose one of two options (A or B) that is most descriptive of them. The factor structure, internal consistency, convergent validity, and reliability of the SSS Form V have been demonstrated numerous times, including a recent large study (Roberti et al., 2003).

Experience Seeking—The experience seeking (ES) subscale measures the tendency to pursue novel behavioral experiences. Individuals who score high on this scale report frequent exploration of new environments, meeting of new people and trying new foods. Two examples are: (1A) “I like to explore a strange city or section of town by myself, even if it means getting lost”, versus (1B) “I prefer a guide when I am in a place I don’t know well”; and (2A) “I order the dishes with which I am familiar so as to avoid disappointment and unpleasantness”, versus (2B) “I like to try new foods that I have never tasted before.”

Thrill seeking—The thrill seeking subscale measures the tendency to pursue a variety of dangerous physical activities. Two examples are: (1A) “I like to dive off the high board”, versus (1B) “I don’t like the feeling I get standing on the high board (or I don’t go near it at all)”; and (2A) “I often wish I could be a mountain climber”, versus (2B) “I don’t understand why anyone would risk their necks climbing mountains”.

Disinhibition—The disinhibition subscale measures the tendency toward unrestrained behavior. Individuals who score high on this scale report frequent partying and drinking. Two examples are: (1A) “I like wild uninhibited parties, versus (1B) “I prefer quiet parties with good conversation”; and (2A) “Heavy drinking usually ruins a party because some people get loud and boisterous”, versus (2B) “Keeping the drinks full is the key to a good party.”

Imaging Data Acquisition

Data were collected on a 3T Magnetom Trio MRI scanner (Siemens, Erlangen, Germany). Foam padding was used to minimize head movements within the coil. A high-resolution, 3D anatomic image was acquired using a T-1 weighted magnetization-prepared rapid gradient echo (MP-RAGE) sequence (repetition time [TR] = 2100ms, echo time [TE] = 2.93ms, inversion time [TI] = 1100ms, flip angle [FA] = 12°, field of view [FOV] = 224 × 256 × 192 mm, 1mm isotropic voxels, sagittal partitions). Image acquisition time was approximately 8.8 minutes. The MP-RAGE images were acquired as part of a larger imaging protocol that included an echo-planar sequence.

Image Analysis Method 1: Manual tracing

Manual volumetric measurements were performed using Analyze software (Analyze Version 6.0, Mayo Clinic, Rochester, MN), running on a linux workstation. Manual tracing was performed following a series of preprocessing steps.

Manual tracing preprocessing—First, images were resliced at an angle perpendicular to the long axis of the hippocampal formation to optimize the identification of hippocampal boundaries. Second, images were 3D aligned to correct for minor head rotation. The resliced, aligned images were used to compute manual intracranial area (see below). Finally, images were corrected for scanner induced intensity inhomogeneity and skull-stripped using FSL’s

brain extraction technique (www.fmrib.ox.ac.uk/fsl). Skull-stripping removed scalp, skull, and dura from images, and was performed in order to obtain automated whole-brain volume measurements (see below). Prior to manual tracing, video display images were magnified by a factor of two to enable precise tracing. After boundaries had been delineated on each slice, the total volume within each region of interest (ROI) was computed by multiplying the number of voxels within the ROI by voxel volume in cubic millimeters.

Manual hippocampal measurement—Manual hippocampus volumes were computed for each participant using procedures derived from Jack et al. (1995; 1997). The borders of the hippocampus were traced sequentially from anterior to posterior for each slice in the coronal plane. Hippocampal volumes were traced by a single rater (SM) who was blind to participant's age, sex, and scores on the personality scales. A second rater who was also blind to participant's scores (JC) traced 10 randomly selected data sets to establish inter-rater reliability. The reliability coefficient was 0.95.

The entire anteroposterior extent of the hippocampus was traced, using anatomical guidelines of Jack et al. (1995). Figure 1 illustrates boundaries used to manually trace the hippocampus. The CA-1 through CA-4 sectors of the hippocampus proper, the dentate gyrus, and the subiculum were all included within the boundaries. Due to the difficulty of distinguishing the head of the hippocampus from the overlying amygdala from the coronal plane, this boundary was distinguished in the sagittal plane (Fig 1, panel A). The boundary marker was then transferred to the coronal plane automatically, and used as the anterior border of the hippocampus (Fig 1, panel B). This procedure has been shown to improve inter-rater reliability (deLeon et al., 2004). The medial border was determined by the CSF in the uncus and ambient cisterns. The lateral border was determined by the CSF in the temporal horn of the lateral ventricle. The inferior border was determined by the interface that separates the subicular grey matter from the white matter of the parahippocampal gyrus (Fig 1, panel C). Finally, the posterior border was determined by the point at which the crura of the fornices were in full profile (Fig 1, panel D).

Manual intracranial area measurement—Manual intracranial area (ICA) was computed using the guidelines suggested by Frisoni et al (1999) for normalization of hippocampal volume. ICA was computed on MR images that contained skull (non skull-stripped images). The ICA was traced on a coronal section at the level where the anterior commissure crosses the midline. Tracing surrounded the outline of the supratentorial compartment following the dural and tentorial surfaces, or the cerebral contour in regions where dura was not visible (Eritiaia et al., 2000). Normalized hippocampal volumes were computed by dividing participant's left and right hippocampal volumes by their ICA.

Whole-brain volume measurement—Whole brain volume (WBV) was computed as an independent test of the results from the hippocampal analysis that used ICA for normalization (described above). WBV was computed on the skull-stripped images. In cases where dura matter was still present following skull-stripping, it was removed from images manually using the image edit feature in Analyze. WBV was then computed automatically in Analyze. Normalized hippocampal volumes were computed by dividing each participant's left and right hippocampal volumes by their WBV.

Analysis of manual tracing—Normalized right and left hippocampal volumes were entered as outcome variables in separate multiple regression models, with scores on the experience seeking (ES) scale, age, education, and sex as predictor variables. Models using ICA and WBV normalization were computed separately and compared. In addition, the relationship between ES and manually-traced hippocampal volumes was explored using independent 'extreme groups' t-tests by dividing participants into 'low' and 'high' groups,

based on the subscale's midpoint (participant's with a score of 5 on the ES were excluded from this analysis).

Correlational and 'extreme groups' analyses were also performed to determine whether thrill seeking or disinhibition were associated with hippocampal volume. For the correlational analyses, a nonparametric Spearman rank correlation was performed because scores on the thrill seeking and disinhibition subscales were not normally distributed. The 'extreme groups' analysis was identical to that used with the ES scale, with participants being divided 'low' and 'high' groups, based on each subscale's midpoint.

Image Analysis Method 2: Voxel based morphometry (VBM)

Voxel-based morphometry (VBM) analysis was performed to correlate ES scores with whole-brain, voxel-wise volumetric measurements. The rationale of this approach is to examine local differences in brain tissue while controlling for differences in brain size. Segmentation is performed using a cluster analysis that identifies voxel intensity distributions of particular tissue types, enabling separate statistical analyses of grey, white and cerebrospinal (CSF) tissue classes (Ashburner and Friston, 2005). VBM was performed using the statistical parametric mapping software package (SPM5, <http://www.fil.ion.ucl.ac.uk/spm>) implemented in Matlab 6.5 (Math Works, Natick, MA), running on a linux operating system.

VBM preprocessing—A series of preprocessing steps were performed prior to statistical analysis to enable separate analysis of grey, white and CSF tissue classes. In SPM2, these steps were performed serially and were sometimes referred to as 'optimized VBM' (Good et al., 2001). In SPM5, the preprocessing steps of segmentation, bias correction and spatial normalization are incorporated into a single generative model (Ashburner and Friston, 2005). Estimating the model parameters involves iteration among classification, bias correction and normalization steps, providing improved results over serial applications (Ashburner and Friston, 2005). This single generative model was used here.

MRIs were segmented into grey matter (GM), white matter (WM) and cerebrospinal (CSF) images using SPM5 prior probability templates. The intensity nonuniformity bias correction was applied to aid segmentation by correcting for scanner-induced smooth, spatially varying intensity differences (Ashburner and Friston, 2000). GM and WM images were normalized to their own custom templates in the standard space of the Montreal Neurological Institute (MNI) using a set of non-linear basis functions. A modulation step was also incorporated into the preprocessing model in order to explore regional differences in absolute volume. Modulation compensates for regional adjustments to volume of certain brain regions inherent in nonlinear spatial normalization by multiplying (or modulating) voxel values in the segmented images by the Jacobian determinants derived from the spatial normalization step (Good et al., 2001). As a final preprocessing step, all normalized, segmented, modulated images were smoothed with a 8-mm FWHM isotropic Gaussian kernel.

VBM analysis—The preprocessed GM and WM data were analyzed separately in SPM5 within the framework of the general linear model. A multivariate linear regression model was employed with voxel-wise GM and WM volumes as outcome variables. The predictor variable of interest was the ES subscale score. Other predictor variables included as potential confounds were age, sex, and education. Whole-brain volume (WBV) derived from the manual tracing analysis was also included as a covariate to adjust for global variance in brain size. Second-level, group linear contrasts were then conducted on parameter estimates from the multiple regression analysis to determine if the relationship between ES and voxel-wise GM/WM volumes was significant. The voxel values for each contrast constituted a statistical parametric

map (SPM) of the t statistic. A brain mask was used to exclude voxels outside the brain. Results were thresholded at $p < .001$ uncorrected.

Results

Manual Tracing Analyses

ICA-normalized right hippocampal volume (nRHV) correlated with scores on the ES ($F = 4.8$, $p < 0.05$). Figure 2 presents the regression plot between ES and nRHV, indicating that the correlation was positive ($r = 0.36$). The remaining regressors were uncorrelated with nRHV [age ($p = 0.83$), sex ($p = 0.44$), education ($p = 0.65$)]. The model for normalized left hippocampal volume (nLHV) showed a slight trend for a relationship with scores on the ES ($F = 2.7$, $p = 0.12$). None of the other regressors correlated with nLHV ($p \geq 0.41$).

Both regressions were performed with hippocampal volumes normalized using WBV instead of ICA. The same pattern of results was found, with the only significant relationship being that between scores on the ES and nRHV ($F = 4.2$, $p < 0.05$). Although the effect sizes of these two results were moderate, they reproducibly indicated a relationship between experience seeking and right hippocampus volume.

In addition, this effect was further supported by results from an independent ‘extreme groups’ t -test comparisons that split participants into ‘low’ versus ‘high’ experience seeking groups along the scale’s midpoint (participant’s with a score of 5 on the ES were excluded from this analysis). This analysis included 28 subjects and indicated greater nRHV in ‘high’ than ‘low’ experience seekers [$t(26) = 2.2$, $p < .05$]. The observed relationship between ES and hippocampal volume was not attributable to overall brain size differences between groups because low and high ES groups did not differ in either ICA [$t(26) = 0.89$, $p = .41$], or WBV [$t(26) = 0.42$, $p = .68$].

Correlational and ‘extreme groups’ analyses were also performed to determine whether thrill seeking or disinhibition were associated with hippocampal volume. Results from the Spearman rank correlation analysis indicated that the relationship between thrill seeking and nRHV was not significant ($\rho = -0.04$, $n = 40$, $p = .81$), nor was the relationship between disinhibition and nRHV ($\rho = 0.25$, $n = 40$, $p = .24$).

For the ‘extreme groups’ analyses, participants were divided into ‘low’ and ‘high’ groups, based on each subscale’s midpoint. A total of 40 subjects were included in the thrill seeking ‘extreme groups’ analysis and a total of 36 subjects were included in the disinhibition ‘extreme groups’ analysis. Results indicated that ‘high’ versus ‘low’ thrill seekers did not have different hippocampal volumes [$t(38) = 0.21$, $p = .86$], nor did ‘high’ versus ‘low’ disinhibitors [$t(34) = -0.80$, $p = .43$].

VBM Analysis

VBM analysis revealed a correlation between scores on the ES scale and grey matter (GM) volume in an anterior portion of the right hippocampus ($p < 0.001$, 58 contiguous voxels) that could not be accounted for by age, sex, education or ICA. The location of the regional volumetric effect (MNI peak: 26 –12 –16) is presented in Figure 3 on the canonical MNI template (panel A) and SPM’s single subject, 3D rendered surface (panel B). No other regional volumetric effect of ES was observed in GM regions. The parallel analysis conducted on WM images did not reveal any regional volumetric effects. These results cross-validate the relationship between experience seeking and nRHV obtained from the manual tracing analysis and localize the peak of this effect to an anterior portion of hippocampal GM.

Discussion

The present results provide evidence for increased right anterior hippocampal volume in experience-seekers. Experience-seekers were defined by their responses on a validated personality scale of this trait, which measures the degree of interest in pursuing novel experiences and stimuli (Zuckerman et al., 1978). The experience seeking-hippocampus relationship was demonstrated using separate analyses conducted independently by two experimenters. In one analysis, hippocampal volumes were traced manually using standard boundary guidelines, which include both grey matter (GM) and white matter (WM). Results indicated a positive correlation between experience seeking and normalized right hippocampal volume. A separate analysis was performed using voxel-based morphometry to (i) test the validity of the manual tracing results, (ii) determine if the effect was primarily associated with grey matter (GM) or white matter (WM) volume, and (iii) explore the possibility that experience seeking may correlate with volume of brain regions outside the hippocampus. The VBM analysis confirmed the results from the manual tracing analysis and localized the positive correlation to an anterior portion of right hippocampal GM.

We do not conclude that differences in right hippocampal volume can alone account for experience seeking. As with any behavior, experience seeking is likely to be determined by multiple factors. These factors may include regional structure, neurochemical profile, receptor expression, and synaptic connection patterns in the brain. Event-related potential (ERP) studies have demonstrated that novel stimuli elicit both an anteriorly oriented P3a and a posteriorly oriented P3b, implicating both prefrontal cortex and posterior regions in novelty processing (Cycowicz & Friedman, 2004; Gaeta et al., 2003). Similarly, functional neuroimaging studies have reported activation of both prefrontal and medial temporal lobe regions in novelty processing (reviewed in Nyberg, 2005). However, because we found a relationship between experience seeking and regional brain volume restricted to the hippocampus, we focus the remainder of our discussion to the role of hippocampus in experience seeking.

Results from the regression analyses allow for exclusion of the possibility that the present experience seeking-hippocampus effect is driven by participants at only one end of the continuum of the experience seeking trait. This scenario would be possible if the comparison between 'high' and 'low' experience seekers was the only one to yield significant results. If this were the case, greater hippocampal volume in the 'high' group compared to the 'low' group could result from the low group having small hippocampal volume and the high group having 'average' hippocampal volume. However, results from our correlational analysis preclude this possibility, demonstrating that the volume of participants' right hippocampus tends to increase as experience seeking behavior increases.

We also examined the possibility that increased hippocampal volume was associated with other components of sensation seeking in addition to the tendency to pursue novelty. There was no relationship between either thrill seeking or disinhibition and hippocampal volume in our sample. The thrill seeking and disinhibition scales assessed the tendency to engage in behavior that is dangerous (thrill seeking) or socially unrestrained (disinhibition), whether those behaviors are novel or not (Zuckerman et al., 1978; Zuckerman, 1994). Our results therefore suggest a specific association between hippocampal volume and interest in novelty. The previously demonstrated reliability and validity of the scales used, and the replication of our results using multiple analysis methods, support the validity of this finding.

The increased hippocampal size was right-lateralized in this study (although there was a slight trend for a relationship between experience seeking and left hippocampal volume). In general, the lateralized effect is in keeping with results from functional neuroimaging experiments in which novelty related medial temporal lobe activity has typically been right lateralized (Nenov

et al., 1994; Tulving et al., 1994; but see Dolan and Fletcher, 1997). The general trend of this finding has led to the suggestion that right medial temporal lobe plays a more salient role in novelty detection/processing than left medial temporal lobe (Martin, 1999). Our results are in good agreement with this suggestion.

The anterior focus of the increased hippocampal volume we observed also warrants consideration. Maguire et al. (2000) showed that the amount of time spent as a taxi driver correlated positively with volume of only one region of the brain: posterior GM of the right hippocampus (peak correlation at 22 –33 3). Draganski et al. (2006) reported an increase in GM volume in posterior hippocampi bilaterally (and in inferior parietal cortex) associated with learning before an intensive medical school examination (peak: 38, –35, –6). It is noteworthy that both of these studies demonstrated a relationship between posterior hippocampal volume and learning (whether the material was visuospatial or a combination of verbal and visuospatial). In contrast, the location of our finding was significantly more anterior (peak: 26 –12 –16) than those reported in these morphometric studies of learning. Together, these findings suggest an anatomically based distinction between anterior-posterior hippocampal regions, along the lines of novelty processing-learning.

Functional neuroimaging studies have supported the concept of an anterior-posterior, novelty detection-learning hippocampal gradient in humans. A meta-analysis of PET studies (Lepage et al., 1998) indicated that activations associated with novelty detection were located primarily in anterior hippocampus, whereas activations associated with processing familiarity of stimuli relevant to learning were located primarily in posterior hippocampus. Similarly, Strange et al. (1999) found an anterior hippocampal response to novel perceptual and semantic components of verbal material and a posterior hippocampal response as semantic components became more familiar. Finally, Tulving et al. (1996) reported that novel versus familiar pictures of people, scenes, and landscapes resulted in prominent functional activation of the right anterior hippocampus. Our results demonstrate an anatomic component to the relationship between anterior hippocampus and novelty processing, concordant with these functional neuroimaging studies.

The distinction between anterior and posterior hippocampal regions should not be taken absolutely, however, because there is an intimate association between indexing novelty and encoding/learning. Novel events tend to become more effectively encoded into long-term memory than familiar events (Kinsbourne & George, 1974; Tulving and Kroll, 1995). Experience seekers tend to seek novel stimuli and experiences and are therefore likely to spend more time than other people actively encoding information into long-term memory. Thus, it is possible that increased memory encoding (which may result from increased indexing of novelty) could contribute to variation in anterior hippocampal volume. However, this possibility remains speculative because our results only provide evidence for a relationship between spontaneously indexing novelty and anterior hippocampal volume.

Increased hippocampus size in experience seekers could have a genetic or developmental basis. One possibility is that experience seekers are born with a relatively large hippocampus, predisposing them to pursue novelty. A second possibility is that experience seekers are born with an average size hippocampus and that differences in dopamine (DA) pathway development or regulation could result in experience seeking behavior which, in turn, could affect the extent of hippocampal growth during development. Genetically determined differences in regulation of DA in experience seekers are well established (Benjamin et al., 1996; Ebstein et al., 1996). On this account, increased exposure to novel environments could cause an increase in hippocampus volume through neurogenesis and/or dendritic or axonal arborization. Neurogenesis has been demonstrated in the hippocampus (Eriksson et al., 1998), and this process can be behaviorally modulated (Kempermann and Gage, 1998; Gage, 2002).

Wiskott et al. (2006) have hypothesized that frequent exposure to novel environments causes an increase in hippocampal neurogenesis.

Finally, the finding of a positive correlation between human experience seeking and hippocampal size in young adults raises the possibility of an adaptive component of this trait in aging. The extent of hippocampal volume reduction and associated memory decrement is variable in aging. The experience-seeker's tendency to spontaneously index and encode novelty may be neuroprotective. For example, in rodent studies, the influence of novelty on synaptic plasticity in the hippocampus was found to extend several minutes beyond the exploration of novelty, raising the possibility that hippocampus-related memory function might be improved in the context of novelty processing (Li et al, 2003). Similarly, a recent human study reported that cognitively high performing elders spent more time spontaneously viewing novel compared to familiar stimuli than did cognitively average performing elders (Daffner et al., 2006). Future research will be required to explore whether an experience seeking personality may serve as one variable that promotes 'successful' aging through protection of hippocampus and memory function.

Acknowledgments

This research was supported by National Institutes of Health grant P50 DA05312. The authors thank Christine Corbly, Kathryn Bylica and Dave Powell for help with data collection.

References

- Ashburner J, Friston KJ. Voxel-based morphometry--the methods. *Neuroimage* 2006;11:805–21. [PubMed: 10860804]
- Benjamin J, Li L, Patterson C, Greenberg BD, Murphy DL, Hamer DH. Population and familial association between the D4 dopamine receptor gene and measures of Novelty Seeking. *Nature Genetics* 1996;12:81–84. [PubMed: 8528258]
- de Leon MJ, DeSanti S, Zinkowski R, Mehta PD, Pratico D, Segal S, Rusinek H, Li J, Tsui W, Saint Louis LA, Clark CM, et al. Longitudinal CSF and MRI biomarkers improve the diagnosis of mild cognitive impairment. *Neurobiol Aging* 2006;27:394–401. [PubMed: 16125823]
- Cycowicz YM, Friedman D. The old switcheroo: When target environmental sounds elicit a novelty P3. *Clinical Neurophysiology* 2004;115:1359–1367. [PubMed: 15134703]
- Daffner KR, Ryan KK, Williams DM, Budson AE, Rentz DM, Wolk DA, Holcomb PJ. Increased responsiveness to novelty is associated with successful cognitive aging. *J Cog Neurosci.* 2006
- Dolan RJ, Fletcher PC. Dissociating prefrontal and hippocampal function in episodic memory. *Nature* 1997;388:582–585. [PubMed: 9252188]
- Draganski B, Gaser C, Kempermann G, Kuhn HG, Winkler J, Buchel C, May A. Temporal and spatial dynamics of brain structure changes during extensive learning. *J Neurosci* 2006;26:6314–7. [PubMed: 16763039]
- Ebstein RP, Novick O, Umansky R, Priel B, Osher Y, Blaine D, Bennett ER, Nemanov L, Katz M, Belmaker RH. Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of Novelty Seeking. *Nature Genetics* 1996;1:78–80. [PubMed: 8528256]
- Eritaia J, Wood SJ, Stuart GW, Bridle N, Dudgeon P, Maruff P, Velakoulis D, Pantelis C. An optimized method for estimating intracranial volume from magnetic resonance images. *Magnetic Resonance in Medicine* 2000;44:973–977. [PubMed: 11108637]
- Flicker C, Geyer MA. Behavior during hippocampal microinfusions. I. Norepinephrine and diversive exploration. *Brain Research* 1982;257:79–103. [PubMed: 6277439]
- Fried I, MacDonald KA, Wilson CL. Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. *Neuron* 1997;18:753–765. [PubMed: 9182800]
- Frisk V, Milner B. The role of the left hippocampal region in the acquisition and retention of story content. *Neuropsychologia* 1990;28:349–59. [PubMed: 2111523]

- Frisoni GB, Laakso MP, Beltramello A, Geroldi C, Bianchetti A, Soininen H, Trabucchi M. Hippocampal and entorhinal cortex atrophy in frontotemporal dementia and Alzheimer's disease. *Neurology* 1998;52:91–100. [PubMed: 9921854]
- Gaeta H, Friedman D, Hunt G. Stimulus characteristics and task category dissociate the anterior and posterior aspects of the novelty P3. *Psychophysiology* 2003;40:198–208. [PubMed: 12820861]
- Gage FH. Neurogenesis in the adult brain. *J Neurosci* 2002;22:612–613. [PubMed: 11826087]
- Good CD, Johnsrude I, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. *NeuroImage* 2001;14:685–700. [PubMed: 11506541]
- Hamer, D.; Copland, P. *Living with our genes: Why they matter more than you think*. Anchor Books; New York, NY, USA: 1998.
- Hoyle RH, Stephenson MT, Palmgreen P, Lorch EP, Donohew RL. Reliability and validity of a brief measure of sensation seeking. *Personality and Individual Differences* 2002;32:401–414.
- Jack CRJ, Theodore WH, Cook M, McCarthy G. MRI-based hippocampal volumetrics: data acquisition, normal ranges, and optimal protocol. *Magnetic Resonance Imaging* 1995;13:1057–1064. [PubMed: 8750317]
- Jack CRJ, Petersen RC, Xu YC, Waring SC, O'Brien PC, Tangalos EG, et al. Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. *Neurology* 1997;49:786–794. [PubMed: 9305341]
- Kempermann G, Gage FH. Closer to neurogenesis in adult humans. *Nat Med* 1998;4:555–557. [PubMed: 9585224]
- Kinsbourne M, George J. The mechanism of the word-frequency effect on recognition memory. *Journal of Verbal Learning & Verbal Behavior* 1974;13:63–69.
- Knight RT. Contribution of human hippocampal region to novelty detection. *Nature* 1996;383:256–259. [PubMed: 8805701]
- Lemon N, Manahan-Vaughan D. Dopamine D1/D5 receptors gate the acquisition of novel information through hippocampal long-term potentiation and long-term depression. *J Neurosci* 2006;19:7723–7729. [PubMed: 16855100]
- Lisman JE, Grace AA. The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron* 2005;46:703–13. [PubMed: 15924857]
- Legault M, Wise RA. Novelty-evoked elevations of nucleus accumbens dopamine: dependence on impulse flow from the ventral subiculum and glutamatergic neurotransmission in the ventral tegmental area. *Eur J Neurosci* 2001;13:819–28. [PubMed: 11207817]
- Lepage M, Habib R, Tulving. Hippocampal PET activations of memory encoding and retrieval: the HIPER model. *Hippocampus* 1998;8:313–322. [PubMed: 9744418]
- Li S, Cullen WK, Anwyl R, Rowan MJ. Dopamine-dependent facilitation of LTP induction in hippocampal CA1 by exposure to spatial novelty. *Nat Neurosci* 2003;6:526–531. [PubMed: 12704392]
- Maguire EA, Gadian DG, Johnsrude IS, Good CD, Ashburner J, Frackowiak RSJ, Frith CD. Navigation-related structural change in the hippocampi of taxi drivers. *PNAS* 2000;97:4398–4403. [PubMed: 10716738]
- Martin A. Automatic activation of the medial temporal lobe during encoding: Lateralized influences of meaning and novelty. *Hippocampus* 1999;9:62–70. [PubMed: 10088901]
- Nenov VI, Halgren E, Mandelkern M, Smith ME. Human brain metabolic responses to familiarity during lexical decision. *Hum Brain Map* 1994;1:249–268.
- Nyberg L. Any novelty in hippocampal formation and memory? *Curr Opin Neurol* 2005;18:424–428. [PubMed: 16003119]
- O'Kane G, Insler RZ, Wagner AD. Conceptual and perceptual novelty effects in human medial temporal cortex. *Hippocampus* 2005;15:326–32. [PubMed: 15490462]
- Reuter M, Hennig J. Association of the functional catechol-O-methyltransferase VAL158MET polymorphism with the personality trait of extraversion. *Neuroreport* 2005;16:1135–1138. [PubMed: 15973162]

- Roberti JW, Storch EA, Bravata E. Further psychometric support for the sensation seeking scale—Form V. *Journal of Personality Assessment* 2003;81:291–292. [PubMed: 14638454]
- Smith ML, Milner B. The role of the right hippocampus in the recall of spatial location. *Neuropsychologia* 1981;19:781–93. [PubMed: 7329524]
- Strange BA, Fletcher PC, Henson RNA, Friston KJ, Dolan RJ. Segregating the functions of the human hippocampus. *PNAS* 1999;96:4034–4039. [PubMed: 10097158]
- Tulving E, Markowitsch HJ, Kapur S, Habib R, Houle S. Novelty encoding networks in the human brain: positron emission tomography data. *NeuroReport* 1994;5:2525–2528. [PubMed: 7696595]
- Tulving E, Kroll N. Novelty assessment in the brain and long-term memory encoding. *Psychonomic Bulletin & Review* 1995;2:387–390.
- Tulving E, Markowitsch MJ, Craik FIM, Habib R, Houle S. Novelty and familiarity activations in PET studies of memory encoding and retrieval. *Cereb Cortex* 1996;6:71–79. [PubMed: 8670640]
- Wiskott L, Rasch MJ, Kempermann GA. A functional hypothesis for adult hippocampal neurogenesis: Avoidance of catastrophic interference in the dentate gyrus. *Hippocampus* 2006;16:329–342. [PubMed: 16435309]
- Yamaguchi S, Hale LA, D'Esposito MD, Knight RT. Rapid prefrontal-hippocampal habituation to novel events. *J Neurosci* 2004;24:5356–5363. [PubMed: 15190108]
- Yang CR, Mogenson GJ. Hippocampal signal transmission to the pedunculo pontine nucleus and its regulation by dopamine D2 receptors in the nucleus accumbens: an electrophysiological and behavioural study. *Neuroscience* 1987;23:1041–1055. [PubMed: 2963972]
- Zuckerman M, Eysenck S, Eysenck HJ. Sensation seeking in England and in America: cross-cultural, age, and sex comparisons. *Journal of Consulting and Clinical Psychology* 1978;46:139–149. [PubMed: 627648]
- Zuckerman M, Kuhlman D, Joireman J, Teta P, Kraft M. A comparison of three structural models for personality: The Big Three, the Big Five, and the Alternative Five. *Journal of Personality and Social Psychology* 1993;65:757–768.
- Zuckerman, M. Behavioral expressions and biosocial bases of sensation seeking. New York: Cambridge University Press; 1994.

Fig. 1.

Anatomical boundaries used for manual tracing of the hippocampus. (A) The boundary between hippocampal head (HH) and amygdala (Am) was demarcated in sagittal plane, where the alveus (denoted by arrow) can be seen to clearly divide the two structures. (B) The automatic transfer of the alveus (denoted by arrow) position from the sagittal plane to the coronal plane was performed to indicate the first slice of the hippocampal head (HH) to be traced. (C) The hippocampal body (HB) is seen on a slice posterior to that shown in panel B. The white matter of the parahippocampal gyrus (denoted by arrow) represents the inferior hippocampal boundary. (D) The hippocampal tail (HT) is seen on a slice posterior to that shown in panel C. The crus of the fornix (denoted by arrow) represented the posterior boundary of the hippocampus.

Fig. 2.

Experience seeking correlates with normalized hippocampal volume. The regression plots participant's experience seeking scores, based on the ES scale, against their ICA-normalized right hippocampal volume (nRHV). There is a positive correlation between ES and nRHV ($r = .36, p < .05$).

Fig. 3.

Experience seeking correlates with VBM-derived hippocampal grey matter volume. Maps depict voxels showing a positive correlation with experience seeking scores, after the global intracranial variance has been removed. A single grey matter voxel cluster ($p < .001$ uncorrected, 58 contiguous voxels; peak: 26 -12 -16) is seen in right hippocampus in yellow on (A) the canonical MNI template. The color bar represents the T score; the crosshair indicates the voxels of maximum effect. The same voxel cluster is shown in red (B) on SPM's single subject, 3D rendered surface.