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Anterior-Posterior Cerebral Blood Volume Gradient in Human Subiculum

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Abstract

The human hippocampal formation is characterized by anterior-posterior gradients of cell density, neurochemistry and hemodynamics. In addition, some functions are associated with specific subfields (subiculum, CA1–4, dentate gyrus) and regions (anterior and posterior). We performed contrast-enhanced, high-resolution T1-weighted 3T steady state (SS) imaging to investigate cerebral blood volume (CBV) gradients of the hippocampal formation. We studied 14 healthy subjects and found significant CBV gradients (anterior > posterior) in the subiculum but not in other hippocampal subfields. Since CBV is a marker of basal metabolism, these results indicate a greater baseline activity in the anterior compared to the posterior subiculum. This gradient might be related to the role of the subiculum as the main outflow station of the hippocampal formation and might have implications for the mechanisms of neuropsychiatric disorders.

Keywords

Hippocampus; CA1; CA2/3; hilus; CBV

Introduction

The hippocampal formation, an elongated structure in the medial temporal lobe, is crucial for memory formation and affect regulation (Morris, Garrud et al. 1982; Eichenbaum 2004). These functions have been mapped to distinct *subfields* and *regions* within the human hippocampal formation (Small, Schobel et al. 2011). Subfields are defined in coronal sections, whereas regions are defined along the anterior-posterior axis of the hippocampal formation.

The subfields of the hippocampal formation include subiculum, Cornu Ammonis sectors 1–4 (CA1–4) and dentate gyrus. There is considerable evidence for the role of each subfield in the processing of multisensory information towards memory encoding and retrieval. The

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CA1 sector is associated with input integration (comparing old and new stimuli), the CA3 sector with pattern completion (retrieval of information based on partial cues) (Fellini, Florian et al. 2009), and the dentate gyrus with pattern separation (distinguish between similar events at different time periods) (Schmidt, Marrone et al. 2012). These sector-dependent functions may be due to different glutamatergic projections from the entorhinal cortex (EC). Layer II cells from the EC project to the dentate gyrus and CA3 via the topographically-organized perforant pathway: the lateral EC is connected to septal dentate gyrus and CA3 subfields while the medial EC sends projections to temporal dentate gyrus and CA3 subfields (Witter, Wouterlood et al. 2000). However, the rostral-caudal (long) axis of the dentate gyrus and CA3 subfields do receive some projections from both the medial and lateral EC, allowing for diffuse activation of these subfields by the EC (Amaral and Witter 1989; Witter, Wouterlood et al. 2000). In contrast to the EC layer II neurons, cells in layer III project to CA1 and subiculum. The lateral EC is connected to the proximal subiculum and distal CA1 (subiculum-CA1 border) while medial EC projections synapse on neurons in the distal subiculum and proximal CA1, allowing for selective input from the EC (Witter, Wouterlood et al. 2000).

There is also growing evidence that the anterior and posterior regions of the hippocampal formation differ anatomically and functionally (Moser, Moser et al. 1993; Moser and Moser 1998; Kjelstrup, Tuvnes et al. 2002; Bannerman, Rawlins et al. 2004). Along the long axis of the hippocampus, the anterior hippocampus has prominent connections with medial prefrontal cortex, orbitofrontal cortex, and nucleus accumbens. In contrast, the posterior hippocampus has strong connections with dorsolateral prefrontal cortex and retrosplenial/posterior cingulate cortex (Fanselow and Dong 2010). Functionally, the anterior hippocampus is associated with the regulation of mood and affect, while the posterior hippocampus is involved in spatial memory and navigation (Fanselow and Dong 2010; Poppenk and Moscovitch 2011; Demaster, Pathman et al. 2013).

In addition, there are cellular, hemodynamic, and neurochemical differences between the anterior and posterior regions of the human hippocampal formation. For instance, pyramidal cell density increases in an anterior-posterior direction (Mouritzen Dam 1979). This is related to findings from proton magnetic resonance spectroscopy studies, which found a similar anterior-posterior gradient of increasing *N*-acetylaspartate (NAA), choline, and creatine (Cre) levels (King, Glodzik et al. 2008; Ostojic, Kozic et al. 2010). In addition, blood supply differs between the two regions: the anterior hippocampus is perfused by the anterior hippocampal branch of the posterior cerebral artery and branches of the anterior choroidal arteries, while the middle and posterior hippocampal branches of the posterior cerebral artery perfuse the posterior hippocampus (Huang and Okudera 1997). This may explain differences in perfusion along the long axis of the hippocampus. A rodent arterial spin labeling (ASL) study has illustrated longer arterial transit times (ATT, 316 vs 244 ms) and lower regional cerebral blood flow (rCBF, 158 vs 173 mL/100 g/min) in the anterior compared to the posterior hippocampus (Thomas, Lythgoe et al. 2006). A recent ASL study has shown a similar gradient in humans, with the ATT and rCBF of 546 ms and 39 mL/100 g/min, respectively, in the anterior hippocampus and 443 ms and 70 mL/100 g/min, respectively, in the posterior hippocampus (Li, Sarkar et al. 2013).

Several neurological and psychiatric disorders, including Alzheimer's disease (Hyman, Van Hoesen et al. 1984; Ball, Fisman et al. 1985), Parkinson's disease (Braak, Braak et al. 1996; Galvin, Uryu et al. 1999), and schizophrenia (Heckers 2001; Heckers and Konradi 2010), are associated with abnormalities of the hippocampal formation. Recent studies have explored whether these disorders affect the subfields of the hippocampal formation differentially (Small, Schobel et al. 2011). An initial study by Schobel et al. reported increased cerebral blood volume (CBV) in the CA1 region of the hippocampal formation in subjects who convert from a high-risk state for psychosis to schizophrenia (Schobel, Lewandowski et al. 2009). Recently the same investigators examined CBV along the long axis of the hippocampus and found increased CBV in the anterior but not posterior CA1 region in patients at-risk for schizophrenia (Schobel, Chaudhury et al. 2013).

Given the notable gradients in cell density, proton spectroscopy, and blood flow across the long axis of the hippocampus, we hypothesized that the hippocampal formation has anatomically unique hemodynamics that reflect the distinct underlying neural activity and chemical structures. Furthermore, it is likely that these distinctions may be subfield specific within the hippocampal formation. While blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) (Szaflarski, Holland et al. 2004; Restom, Bangen et al. 2007; Bangen, Restom et al. 2009) and arterial spin labeling (Restom, Bangen et al. 2007; Bangen, Restom et al. 2009; Rusinek, Brys et al. 2011) are well-established approaches to evaluate hippocampal function, contrast-enhanced steady state imaging offers a unique advantage to perform sub-millimeter CBV mapping (Lin, Celik et al. 1999). CBV measures microvasculature blood volume and has been well-established as a marker of basal metabolism (Small, Schobel et al. 2011). Steady state CBV utilizes high resolution imaging that reduces partial volume effects, improves segmentation, and allows for CBV measurement in the hippocampal subfields (Small, Schobel et al. 2011). Therefore, we performed contrast enhanced, high resolution T1-based steady state (SS) imaging in 14 healthy controls to examine an anterior-posterior CBV gradient in the human hippocampal formation.

For each subject, we manually segmented ROIs for the whole hippocampal formation and different subfields (subiculum, CA1, CA2/3, and hilus) along the long axis of the hippocampus (see Figure 1 for a representative subject). The CBV values averaged across the long axis of the hippocampus (mean $\pm$ standard deviation; units = ml blood/ml parenchyma) for whole hippocampal formation, subiculum, CA1, CA2/3, and hilus were 3.22 ± 0.61 , 3.07 ± 1.12 , 3.58 ± 0.89 , 2.84 ± 0.94 , 2.89 ± 1.03 (left hippocampal formation) and 3.40 ± 0.57 , 3.15 ± 1.24 , 2.66 ± 0.83 , 3.07 ± 1.21 , 3.12 ± 0.91 (right hippocampal formation). These values are similar to those reported previously for cerebral cortex (Sakaie, Shin et al. 2005) and hippocampus (Kuppusamy, Lin et al. 1996).

Each subject's CBV values were plotted along the long axis of the hippocampal formation, moving from the most anterior (slice two) to the most posterior slice (slice seven) (Figure 2). A linear fit to the data provided a gradient value for each subject. The group average was used to test the hypothesis of an anterior-posterior CBV gradient. We found significant gradients in the right (two-tailed t-test, $p < 0.01$) and left ($p < 0.01$) hippocampal formation. The slope values (mean $\pm$ standard deviation; units = (ml blood/ml parenchyma)/4mm³)

were -0.096 ± 0.13 and -0.095 ± 0.12 for the left and right hippocampus, respectively (Figure 2).

We tested whether the CBV gradient differed between the subfields of the hippocampal formation. The slope values for the subiculum, CA1, CA2/3, hilus were -0.20 ± 0.23 , 0.05 ± 0.24 , -0.06 ± 0.24 , -0.093 ± 0.35 in the left hippocampal formation and -0.36 ± 0.33 , 0.0065 ± 0.20 , -0.030 ± 0.31 , 0.016 ± 0.29 in the right hippocampal formation. The results illustrate a significant anterior-posterior CBV gradient in the right subiculum (two tailed t-test, $p < 0.0005$, corrected for multiple comparisons) and left subiculum (two-tailed t-test, $p < 0.005$, corrected for multiple comparisons), but not the other subfields (Figure 3). To better characterize the gradients, average subject CBV was calculated for the 5 ROIs for each slice along the long axis of the hippocampus. The line curve trend, along with the line of best fit, for the hippocampal formation and its subfields are shown in Supplementary Figure 1.

Finally, we investigated whether the significant gradients were influenced by age, gender, or race. Our results indicate that the right and left hippocampal CBV gradients did not correlate with age ($p = 0.449$ and $p = 0.098$) or race ($p = 0.228$ and $p = 0.470$). Right hippocampal CBV did not correlate with gender ($p = 0.830$) but left hippocampal CBV did ($p = 0.033$). The right and left subiculum CBV gradients did not correlate with age ($p = 0.641$ and $p = 0.646$), gender ($p = 0.325$ and $p = 0.080$), or race ($p = 0.948$ and $p = 0.909$).

Since CBV is a marker of basal metabolism, the results of this study indicate greater anterior than posterior activity of the human subiculum. Considering the role of the subiculum as the main outflow station of the hippocampal formation (O'Mara 2005), such a gradient might have functional implications (Lisman and Grace 2005). Within the subiculum, burst cells are organized into columns, and regular spiking neurons integrate columnar activity along the transverse axis (Poppenk and Moscovitch 2011). The intrinsic circuitry of the subiculum, mainly the burst cells, may predispose to epileptiform activity and epileptogenesis (Stafstrom 2005). Along the long axis of the subiculum, the ventral (anterior) subiculum projects to the medial entorhinal cortex, amygdala, and the bed nucleus of the stria terminalis while the dorsal (posterior) subiculum projects to the lateral entorhinal, retrosplenial, and perirhinal cortices (Andersen 2007). Functionally, the anterior subiculum plays a major role in inhibiting the stress response through the hypothalamic-pituitary-adrenal (HPA) axis while the posterior subiculum processes information about memory, movement, and spatial direction (O'Mara 2005). Subicular inhibition of the HPA axis is thought to be mediated through γ -aminobutyric acid (GABA) (Lowry 2002; Herman, Mueller et al. 2004), and tonic inhibition would indeed lead to increased CBV in the anterior subiculum. The posterior subiculum CBV values may be low due to the nature of the study: participants were told to lie still in the scanner and a scan was obtained without performing a task. Thus, many of the key functions of the posterior subiculum may have not been recruited, including memory and spatial direction. Future studies should examine whether task performance modulates the CBV gradient in the subiculum.

Anterior-posterior gradients of the hippocampal formation have been explored in aging, depression, ischemia, and neurogenesis. Normal aging has been reported to cause reductions

in posterior, but not anterior, hippocampal volume (Driscoll, Hamilton et al. 2003). In contrast, depression has been linked to anterior hippocampal volume reduction, possibly due to decreased neuropil and glial cell number in CA1 and dentate gyrus (Willard, Friedman et al. 2009; Willard, Riddle et al. 2013). Within CA1, there is a notable anterior-posterior ischemia susceptibility gradient, with the posterior region (dorsal hippocampus in rodents) being more vulnerable to ischemia than the anterior region (ventral hippocampus in rodents) (Ashton, Van Reempts et al. 1989). Finally, in rodents, adult neurogenesis was higher in the dorsal, compared to ventral, dentate gyrus and significantly increased after performing a spatial task (Snyder, Radik et al. 2009). Further studies need to explore how neuropsychiatric disorders such as schizophrenia can disrupt the normal anterior-posterior gradients of basal metabolism in the subiculum.

This study has several limitations. The sample size is small (but consistent with previous CBV imaging studies) and the cohort included both genders, different races, and mostly right-handed subjects. While our results show that the CBV gradients are independent of age and race, gender was significantly correlated with left hippocampal but not left subicular CBV.

In conclusion, we found a significant anterior-posterior CBV gradient in the human subiculum. Future studies should investigate the functional implications of this gradient for normal hippocampal function and possible alterations in disease states.

DETAILED METHODS

Participants

14 healthy subjects (nine male, five females; age range: 23–53 years; mean age $\pm$ st. dev: 35.14 ± 8.72 years) provided informed consent as approved by the Institutional Review Board (see Table 1 for subject demographics). Using a structured clinical interview (SCID-I/P (First November 2002)), we excluded any major medical, psychiatric, or neurological illness. In order to minimize the risk of nephrogenic systemic fibrosis, serum creatinine was measured before and 24–48 hours after contrast administration to ensure normal kidney function (GFR > 60).

Cerebral Blood Volume Mapping

Imaging was performed using an 8 channel SENSE head coil with a Philips 3T Achieva scanner. T1-weighted pre- and post-contrast images were acquired using a 3D T1 FFE (Lin, Celik et al. 1999) sequence with the following imaging parameters: TR/TE = 20 ms/3.98 ms, FOV = 256×256 mm², Res = $0.80 \times 0.80 \times 4$ mm³, slices = 30, SENSE factor = 2.5. Post-contrast images were acquired approximately four minutes after contrast administration (Magnevist® - Gadopentate dimeglumine, Bayer Schering Pharma, Germany, 0.1 mmol/kg). Contrast was administered using a power injector (Medrad®, PA, USA) through the antecubital vein with an 18G needle and was followed by a 40 ml saline flush. Images were acquired perpendicular to the long axis of the hippocampus to allow for accurate segmentation of the hippocampal subfields as briefly outlined below and referenced in (Moreno, Wu et al. 2007). Of note, the boundary between subfields can only be determined

through histological landmarks and were excluded from the regions of interest (ROIs). We compared the local fractional increase in tissue signal after a gadolinium-containing intravenous contrast agent had equilibrated in the blood and thoroughly perfused the microvasculature.

Analysis

CBV calculations—The pre- and post-contrast steady state images were corrected for subject motion using AFNI (2dimreg) (Cox 1996). Absolute CBV in the brain was measured by subtracting the pre-contrast from the post-contrast image, normalized by the difference in the superior sagittal sinus (Lin, Celik et al. 1999). A 10% regional CBV threshold was used to minimize large epicortical vessel contribution (Lin, Celik et al. 1999). Analysis was completed using Matlab (version 7.13.0., The MathWorks Inc, Natick, Massachusetts).

Hippocampal Segmentation—Manual segmentation of the subiculum, CA1 sector, CA2/3 sector, and the hilus (CA4 with some dentate gyrus contribution) was performed by one rater (PT) using the pre-contrast image. The post-contrast image was used as a guide to ensure epicortical vessels were excluded. A separate ROI was drawn to segment the whole hippocampus (defined as containing the subiculum, CA1–4, and dentate gyrus) in each slice. We chose manual segmentation of each hippocampus in the native space instead of co-registration to a standard space to minimize interpolation in older subjects who may have a smaller hippocampus. We were able to segment all 5 regions of interest in 6 to 8 slices in all subjects. There were some slices in the anterior-most or posterior-most hippocampus that were not included because they could not be segmented due to methodological limitations (unclear subfield boundaries). ROI placement was verified with another rater (SR). In case of discrepancies, both raters redrew the ROI until a consensus was reached.

We used the uncus to delineate the anterior and posterior regions of the hippocampal formation. The uncus can be defined in coronal sections as more than one cut through the hippocampus (Duvernoy and Bourgouin 1998; Woolard and Heckers 2012). We numbered the coronal series for each subject in such a way that the same section corresponded to the same region of the hippocampal formation. In most subjects, the hippocampal subfields could not be segmented in slices one and eight, and they were not included in the analysis. Three slices (slices two-four) were identified as anterior hippocampus and three slices (slices five-seven) as posterior hippocampus. The transition from slice four to slice five denotes the anterior-posterior boundary of the hippocampal formation.

CBV Gradient Determination—For each aligned slice of the hippocampus, CBV values were calculated in the four subfields and in the whole hippocampus for all subjects. Outliers were detected at each slice using Tukey's method (Tukey 1977). Interquartile range (IQR) was calculated using the 25th and 75th percentile of CBV measurements. Values $> 1.5 \times \text{IQR}$ were considered as outliers. The CBV values for each subfield in each subject were plotted along the x-axis, starting with slice 2 and ending with slice 7. Slices 2–4 denote the anterior hippocampus and slices 5–7 denote the posterior hippocampus. Slopes were calculated using the line of best fit for each individual subject. Each subject's slope was used to generate an average group slope for gradient comparison.

The Statistical Package for Social Sciences software (SPSS version 20, <http://www.spss.com>) was used to determine whether the CBV slopes/gradients from slice two (the anterior hippocampus) to slice seven (posterior hippocampus) were significant by testing against a null hypothesis of no gradient (slope = 0) using a two-tailed t-test. The Bonferroni method (Lesack and Naugler 2011) was used to correct for multiple comparisons when appropriate. Subsequent correlation analyses were performed between significant CBV gradients and age, race, or gender.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Steady-state 3T imaging (radiological orientation)

A: T1-weighted coronal image containing the anterior hippocampus

B: Figure A with hippocampal formation ROI tracing (red) and subfields (purple = subiculum, red = CA1, blue = CA2/3, green = hilus)

C: Post-contrast image with ROIs overlaid from B.

D: T1-weighted coronal image containing the posterior hippocampus

E: Figure E with hippocampal formation ROI tracing and subfields

F: Post-contrast image with ROIs overlaid from E.

Figure 2. Anterior to posterior gradients in the hippocampus

There is a significant anterior to posterior gradient in the left (two tailed t-test, $p < 0.01$) and right ($p < 0.01$) hippocampus in healthy controls. The gray lines denote slopes for individual subjects, while the black line represents the average slope.

Figure 3. Anterior to posterior gradients in the hippocampal subfields

There is a significant anterior to posterior gradient in the left (two tailed t-test, $p < 0.005$) and right ($p < 0.0005$) subiculum, but not other subfields of the hippocampal formation, in healthy controls. Error bars denote standard error of the mean.

Table 1

Healthy control subject demographics

Gender (n)	Age (yrs) $\pm$ stdev	Race (W/B)	Handedness (L/R)
Males (9)	37.78 $\pm$ 9.37	7/2	1/8
Females (5)	30.4 $\pm$ 5.27	4/1	1/4