

## RAPID COMMUNICATION

## Hippocampal Subregions Differentially Associate With Standardized Memory Tests

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**ABSTRACT:** Recent studies suggest that individual hippocampal subregions perform distinct cognitive operations and are differentially targeted by aging and disease. Although originally developed to assess global hippocampal function, whether performance on standard memory tests used in neuropsychological batteries is associated with individual hippocampal subregions remains unknown. Here we addressed this issue by imaging 210 neuropsychologically characterized subjects using a high-resolution variant of functional magnetic resonance imaging that generates maps reflective of basal hippocampal metabolism. Regression analysis revealed memory tests that differentially associate with two hippocampal subregions, the entorhinal cortex (EC) and the dentate gyrus (DG). Whereas performance on the delayed retention component of the Selective Reminding Test was associated with the EC, performance on the recognition component of the Benton Visual Retention Test (BVRT) was associated with the DG. Furthermore, elevation in blood glucose, previously shown to target the DG, was found to correlate selectively with the recognition component of the BVRT. These findings provide further evidence that the hippocampal subregions perform distinct roles, and, interpreted in the context of previous neuropsychological and imaging studies, confirm that aging and Alzheimer's disease target different hippocampal subregions. © 2010 Wiley-Liss, Inc.

**KEY WORDS:** entorhinal cortex; dentate gyrus; aging

## INTRODUCTION

Nearly all studies investigating the effect aging and disease has on human cognition employ a battery of neuropsychological tests that have been characterized and standardized through decades of experience. Typically, these batteries include memory tests putatively sensitive to the function of the hippocampal formation. Notably, these tests were originally developed to assess global hippocampal function, to contrast with performance on tests sensitive to the function in other general brain areas. Recent studies suggest, however, that each of the

individual subregions that make up the hippocampal formation performs a distinct cognitive and computational operation (Nakazawa et al., 2002; Kent et al., 2007; Leutgeb et al., 2007; McHugh et al., 2007; Bakker et al., 2008; Brun et al., 2008), and that individual subregions are differentially vulnerable to mechanisms of hippocampal dysfunction (West et al., 1994; Small et al., 1999, 2004; Moreno et al., 2007; Wu et al., 2008; Schobel et al., 2009).

Whether standard memory tests used in neuropsychological batteries reflect the function of different hippocampal subregions remains unknown. Addressing this issue is important as it can provide additional evidence that hippocampal function can be parsed according to its individual subregions and can further clarify the distinct roles played by each subregion. Moreover, linking standardized memory tests to individual subregions will enhance the interpretive abilities of neuropsychological studies that have begun characterizing the cognitive profile associated with aging and hippocampal-dependent disorders such as the early stages of Alzheimer's disease.

With these goals in mind, we generated functional maps of the hippocampal formation in 210 neuropsychologically characterized subjects using a variant of functional magnetic resonance imaging (fMRI) that measures basal cerebral blood volume (CBV). As with other functional imaging variables, CBV is hemodynamically coupled to oxygen metabolism (Belliveau et al., 1991; Mandeville et al., 1998, 2001; Shen et al., 2008), and is tightly correlated with other basal measures of brain function, such as cerebral blood flow and deoxyhemoglobin as measured with MRI (Mandeville et al., 1998, 2001; Shen et al., 2008), or glucose uptake as measured with positron emission tomography (Gonzalez et al., 1995). Among all functional imaging approaches, measuring steady-state basal CBV with MRI provides the highest spatial resolution (Lin et al., 1999), a feature that enhances the ability to visualize individual hippocampal subregions. Indeed, previous studies have used CBV mapping to pinpoint dysfunction in select regions of the hippocampal formation in aging (Small et al., 2004), Alzheimer's disease (Moreno et al., 2007), schizophrenia (Schobel et al., 2009), and diabetes (Wu et al., 2008).

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The subjects all received a standard neuropsychological battery that contained a commonly used verbal and nonverbal hippocampal-dependent test, the Selective Reminding Test (SRT) (Buschke and Fuld, 1974), and the Benton Visual Retention Test (BVRT) (Benton, 1994). In the recognition component of the BVRT (Benton recognition), subjects are briefly shown a visual pattern then asked to identify the pattern they saw among three other novel patterns. In the SRT, during an encoding phase subjects first learn a list of words presented aurally, and then after a 15-min delay are asked to freely recall the words. In a previous study using a smaller number of subjects that consisted of 11 Alzheimer's disease patients and 11 controls, we examined "delayed recall," the absolute number of words recalled after the delay (Moreno et al., 2007). Delayed recall, however, reflects both the number of words encoded during the learning phase and the number of words retained during the delay, the latter which is thought to be most sensitive to hippocampal function (Squire et al., 2004). In this study we focused on "delayed retention," derived by normalizing the number of words recalled after delay by the number of words encoded after the learning phase. Delayed retention is particularly interesting because it has been shown to be affected in the earliest stages of Alzheimer's disease, decades before the onset of disease (Elias et al., 2000), and relatively unaffected by aging (Albert, 1997).

After identifying a dissociation linking hippocampal subregions to different memory performance metrics, we then set out to confirm and extend our findings by exploiting previous imaging studies in humans, nonhuman primates, and mice showing that elevations in blood glucose levels targets the dentate gyrus (DG) (Wu et al., 2008). Accordingly, we measured blood glucose levels in subset of subjects and tested for its association with the hippocampal-dependent memory tests.

## METHODS

### Subjects

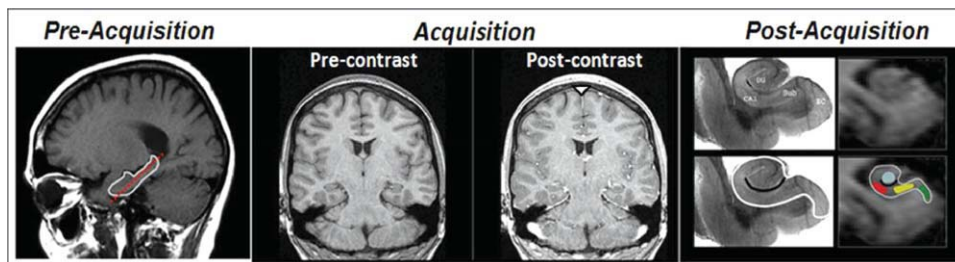
Participants were part of a community-based study of elderly subjects (65 years and old) who together with brain imaging (Brickman et al., in press) received a detailed neuropsychological, neurological, and medical evaluation (Stern et al., 1992). Within this cohort hippocampal CBV, maps were generated in 210 subjects (mean age = 79, 63% female) who had: (a) no evidence of Alzheimer's disease or other neurological disorders, as determined by a consensus conference made up of neurologists and neuropsychologists; (b) no evidence of preclinical Alzheimer's disease, based on a specific cognitive profile of mild cognitive impairment that we have previously found to be indicative of the predementia stage of the disease in this community-based population (Manly et al., 2008). Serum glucose measured in microIU/ml from serum collected within 1 month of the brain MRI and frozen at  $-70^{\circ}\text{C}$ . Glucose levels were measured on a Hitachi automated spectrophotometer (model 704, Hitachi, Tokyo, Japan) using commercial kits obtained from Wako Chemicals (Richmond, VA).

### Memory Tests

The BVRT in an object recognition memory paradigm. Participants view a visual pattern and then are asked to select the target from an array of four patterns, three of which are distracters. There are 10 trials on the task and the relevant outcome variable is the number of correct trials. In each trial, the subject is shown a visual object stimulus for 10 s, it is removed, and then a  $2 \times 2$  array of three foils and one target is displayed. The subject's task is to select the target stimulus, and the number of correctly recognized targets are tallied (Benton recognition). During a 10-trial BVRT *matching* block, subjects are shown the target stimulus and the four-choice array simultaneously. Subjects are asked simply to indicate which of the four stimuli is identical to the target. Stimuli used during the matching trials are distinct from those used in the recognition trials. The SRT (Buschke and Fuld, 1974) was administered to participants to assess verbal learning and memory. Participants are presented with 6 trials to learn 12 semantically unrelated words aurally. After each attempt to recall the list, subjects are reminded only of the words that were not recalled and then asked to recall the entire list ('total recall'). Subjects are asked to recall as many words as possible from the list after a 15-min delay. "Delayed recall" is the total number of words recalled after delay, and "delayed retention" is the total number of words recalled after delay normalized by number of items recalled on the last learning trial.

### Imaging

The technical and analytic details of how CBV maps of the human hippocampal formation were generated has been previously described (Moreno et al., 2007) (Fig. 1). Briefly, a 1.5 Tesla scanner (Philips Intera) was used to acquire oblique coronal 3D T1-weighted images (TR = 20  $\mu\text{s}$ ; TE = 6  $\mu\text{s}$ ; flip angle = 25 degrees; in plane resolution = 0.86 mm  $\times$  0.86 mm; slice thickness = 3 mm), perpendicular to the hippocampal long axis (Fig. 1B), before and 4-min after IV administration of gadolinium-pentate (Omniscan, 0.1 mmol/kg). Then, the postcontrast images were subtracted from precontrast images, and the difference in the superior sagittal sinus, which serves as an estimate of the image intensity change of 100% blood, was recorded (Lin et al., 1999; Moreno et al., 2007). Finally, the subtracted image was divided by the difference in the top four pixels measured from the sagittal sinus and multiplied by 100 yielding percent CBV. In all cases, a single ideal slice was identified, anterior to the lateral geniculate nucleus and posterior to the uncus, which contains all hippocampal subregions and provides sufficient anatomical information to parse the subregions (Moreno et al., 2007) (Fig. 1B). Because spatial coregistration across subjects is problematic when evaluating small regions in clinical populations, strict anatomical criteria (Moreno et al., 2007) were used to identify the following regions-of-interest within the hippocampal formation: The EC, DG, CA1 subfield, and the subiculum. The CA3 subregion cannot be reliably visualized because of age-related atrophy. On



**FIGURE 1.** Mapping cerebral blood volume (CBV) in the hippocampal formation. Left panel: During preacquisition, slices were acquired perpendicular to the long axis of the hippocampus (indicated in red). Middle panel: Images were acquired “pre” and 4-min “post” intravenous injection of gadolinium. Right panel: During postacquisition, anatomical landmarks were used to identify hippocampal regions-of-interest. Upper and lower left panels show histological slice of the hippocampal formation. Upper right panel shows MRI slice of the hippocampal formation, lower right panel shows regions-of-interest. Green = entorhinal cortex; blue = dentate gyrus; red = CA1 subfield; yellow = subiculum.

an individual basis, mean CBV values were measured for each hippocampal ROI and used for group data analysis.

### Data Analysis

To test for an association between cognitive performance and hippocampal subregions, a stepwise multiple regression model was constructed in which cognitive performance was included as the dependent variable, CBV measured from the four hippocampal subregions (EC, DG, CA1, SUB) were included as the independent variables and demographic data (age, gender, ethnicity, and education) were included as covariates.

## RESULTS

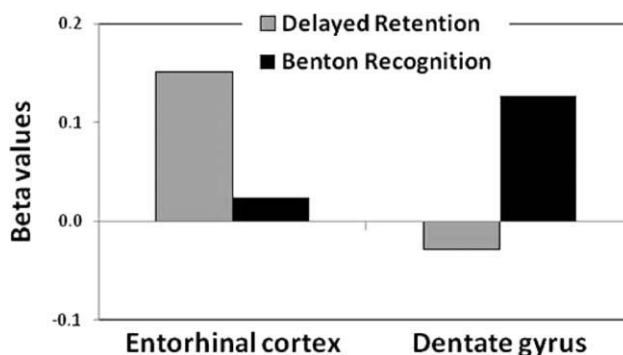
By including the CBV values of hippocampal subregions into a single regression model, the DG was found to be the only hippocampal subregion related to performance on the Benton recognition ( $\beta = 0.13, P = 0.02$ ) (Table 1 and Fig. 2). Among the other hippocampal subregions, CBV measured in the entorhinal cortex (EC), was least associated with performance ( $\beta = 0.02, P = 0.68$ ) (Table 1 and Fig. 2). In contrast, the EC was the only hippocampal subregion linked to delayed retention ( $\beta = 0.15, P = 0.03$ ), while the DG was least associated with performance ( $\beta = -0.03, P = 0.61$ ) (Table 1 and Fig. 2).

**TABLE 1.** Correlations Between CBV Measured in the Hippocampal Subregions and Memory Performance

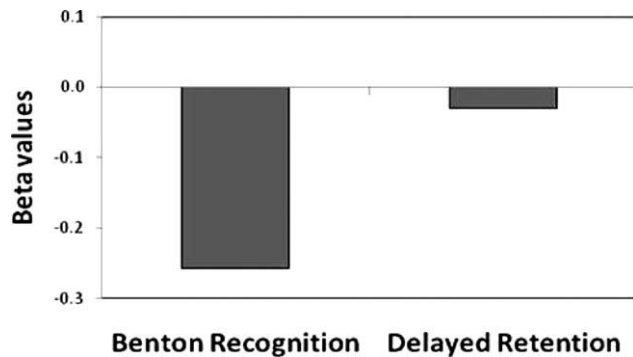
		EC	DG	CA1	SUB
Benton recognition	Correlation	0.02	0.13	-0.06	0.10
	P value	0.68	0.02	0.23	0.08
Delayed retention	Correlation	0.15	-0.03	0.05	0.10
	P value	0.03	0.61	0.45	0.15

campal regions-of-interest. Upper and lower left panels show histological slice of the hippocampal formation. Upper right panel shows MRI slice of the hippocampal formation, lower right panel shows regions-of-interest. Green = entorhinal cortex; blue = dentate gyrus; red = CA1 subfield; yellow = subiculum.

To expand the focus, in a secondary analysis we used a partial correlational model which included the CBV of four hippocampal subregions (EC, DG, CA1, Subiculum), the four components of the SRT (total recall, last-trial recall, delayed recall, and delayed retention), and the two components of the BVRT (recognition and matching), controlling for sex, age, education, and ethnicity. Beyond confirming the specificity of the effects, (Supporting Information Table), this secondary analysis confirmed our previous observation that delayed recall is also associated with EC CBV (correlation coefficient = 0.18;  $P = 0.01$ ). Importantly, immediate recall on the last trial was not significantly correlated with the EC (correlation coefficient = 0.07;  $P = 0.30$ ) or other hippocampal subregions, suggesting that the association between EC and delay retention/recall is dependent on the delay period (i.e., forgetting) per se and not by the amount of information that was encoded. Additionally, there was not a significant association between performance on the BVRT matching trials and DG CBV (correlation coefficient = 0.10;  $P = 0.15$ ) or any other hippocampal subregion, suggesting the association observed with BVRT recognition is not related to potential confounds in visual processing.



**FIGURE 2.** Hippocampal subregions differentially associate with memory tests. Cerebral blood volume (CBV) in the entorhinal cortex was differentially associated with delayed retention, while CBV in the dentate gyrus was differentially associated with the Benton recognition. Y-axis =  $\beta$  values from the regression analysis.



**FIGURE 3.** Blood glucose levels are differentially associated with Benton recognition.

To extend the primary observations, we measured blood glucose levels in 152 of subjects. Regression analysis showed that performance in the Benton recognition, but not performance on delayed retention, was inversely and significantly linked to blood glucose ( $\beta = -0.26$ ,  $P = 0.02$ ) (Fig. 3). In secondary analyses we expanded the correlational analysis, and found no association between blood glucose and any other cognitive measure, including delayed recall (correlation coefficient =  $-0.62$ ;  $P = 0.46$ ), last trial recall (correlation coefficient =  $-0.12$ ;  $P = 0.16$ ), or BVRT matching (correlation coefficient =  $-0.13$ ;  $P = 0.12$ )

## DISCUSSION

Although neuropsychological tests were originally designed without the anatomical complexity of the hippocampal formation in mind, the results of this large-scale fMRI study suggest an anatomical dissociation between delayed retention on a word learning test and immediate recognition of novel visual patterns. Specifically, while delayed free recall/retention was associated with the EC, recognition of visual patterns was associated with the DG. The observation that elevation in blood glucose, previously found to target the DG not the EC, is inversely and selectively correlated with recognition of visual patterns further confirms these findings.

Although it is important to note that the two memory tests differ in many ways, we can interpret our findings in the context of previous studies using nonstandard memory tests that have begun uncovering distinct cognitive operations in individual hippocampal subregions. Influenced by computational and rodent studies (Leutgeb et al., 2007; McHugh et al., 2007), human fMRI studies have established that the DG (Bakker et al., 2008), not the EC, plays an important role in pattern separation. Pattern separation is the computational process by which the hippocampal formation orthogonalizes the neural representation of similar stimuli. Importantly, previous studies have suggested that the cognitive operation that underlies pattern separation begins in the DG, not the EC (Colgin et al., 2008). The recognition component of the BVRT relies heavily

on pattern separation, which can account for why performance on this task was found to associate with a functional measure of the DG. We note, however, that the BVRT was not explicitly designed to test pattern separation, and so this interpretation should be tested in future studies. In particular, a variation of this task that includes a greater number of items that vary by degree of similarity will be able to more formally test for pattern separation effects.

The observation that the EC CBV is selectively linked to delayed retention/recall but not immediate recall suggests that the EC might play a role during the delay period. Interestingly, a convergence of findings has implicated the EC in maintenance of memory representations across a delay. These observations were first found by unit recordings in monkeys and rats (Suzuki et al., 1997; Young et al., 1997), but have recently extended to include numerous human studies. By fMRI, studies have found that sustained EC activation during encoding predicts performance on delayed cue-recall (Fernandez et al., 1999) or delayed recognition (Schon et al., 2005), and that sustained EC activation is observed during the “delay” in a delay-match-to-sample task (Schon et al., 2004). The interpretation that the EC plays an active mnemonic role during the delay phase is mechanistically supported by a unique electrophysiological feature of the EC. Among all subregions, only the EC possesses “persistent firing” neurons (Egorov et al., 2002; Fransen et al., 2004; Tahvildari et al., 2007; Yoshida et al., 2008), cells that are notable for their sustained firing, often many minutes poststimulation and whose persistent firing is relatively resistant to distracters. Together, these two properties are ideally suited to play a role during delay periods, either by acting as a “memory buffer” or by entraining plasticity in downstream subregions.

The importance of our findings is twofold. First, our study is the first to investigate the hippocampal formation using both a delay recall/retention task and a task dependent on pattern separation in the same subjects. The observed dissociation supports the emerging view about the differential roles played by the EC and the DG. At a practical level, our results suggest that standard memory tests used in most neuropsychological batteries can assess the functional integrity of individual hippocampal subregions, even in the absence of imaging or electrophysiological data. These results expand the interpretive power of neuropsychological testing in many studies that investigate the effect of aging and disease has on the hippocampal formation.

This ability is particularly useful in light of evidence showing that any process that causes hippocampal dysfunction typically does so by differentially targeting one hippocampal subregion over another (Small, 2001). Alzheimer’s disease, a progressive process that anatomically spreads over time, is thought to begin in the EC before it spreads to involve other hippocampal subregions (Braak and Braak, 1996). Importantly, a growing number of prospective neuropsychological studies have shown that delayed retention is a cognitive task that is affected in the earliest stages of Alzheimer’s disease—remarkably decades before the onset of dementia (Elias et al., 2000). At the same time, in

contrast to Alzheimer's disease, delayed retention is a hippocampal-dependent task relatively unaffected by aging (Albert, 1996). Thus, by showing that delayed retention differentially localizes to the EC, our results support previous imaging studies showing that the EC is targeted by Alzheimer's disease but spared in normal aging (Small et al., 2004; Moreno et al., 2007).

Over time Alzheimer's disease will involve other hippocampal subregions and therefore it is not surprising that the BVRT and pattern separation tasks are ultimately affected in the disease (Kawas et al., 2003; Yassa et al., 2010). Nevertheless, studies have shown that aging itself will affect the recognition component of the BVRT (Resnick et al., 1995), other visual recognition tasks (Schacter et al., 1992; Grady et al., 1995) and pattern separation (Toner et al., 2009) supporting the conclusion that aging without Alzheimer's disease differentially targets the DG (West et al., 1994; Gazzaley et al., 1996; Small et al., 2004).

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