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RAPID COMMUNICATION

Increased Inhibition and Enhancement of Memory Retrieval Are Associated With Reduced Hippocampal Volume

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ABSTRACT: Putative control of encoding and retrieval processes have been linked to communication between the lateral prefrontal cortex (LPFC) and the hippocampus. Moreover, correlations between the LPFC (e.g., MFG) and hippocampus have predicted individuals' ability to inhibit memory retrieval. Anatomically, differences in volume of the hippocampus have been related to changes in long-term episodic memories. Although the relationship between these ideas is clear, few studies have examined the association of how anatomy may affect the role of control over brain regions involved in distint memory processes. The current study sought to examine hippocampal volume and its relationship to LPFC control over the hippocampus. Using an automated cortical/subcortical segmentation technique (FIRST) on brain imaging gata from the Think/No-Think task, we show that hippocampal volume is associated to changes in both enhancement and inhibitory processes of memory retrival. © **2011 Wiley Periodicals, Inc.**

KEY WORDS: Hippocampus; memory retrieval; inhibition; volume; morphometry

INTRODUCTION

The hippocampal formation is known as critically involved in episodic long-term memory retrieval (Frankland and Bontempi, 2005). Similarly, research has indicated important hippocampal communication with the PFC supporting encoding and subsequent retrieval during controlled memory processes (Wagner et al., 1998; Wagner, 2002; Bunge et al., 2004; Badre et al., 2005; Badre and Wagner, 2007). Numerous studies suggest that the structure or volume of this brain region is related to differences among individuals in the ability to retrieve episodic memories, which has been shown both qualitatively, regarding amount of detail of single episodes; and quantitatively, regarding the overall amount of episodic memory retrieval (Jacobs et al., 1990; Sherry et al., 1993; Maguire et al., 2000). Given that recent neuroimaging studies have suggested that the ability to suppress or inhibit episodic memories is associated with decreased hippocampal activity (Anderson et al., 2004; Depue et al., 2007), the present study examines whether individual differences in hippocampal volume may also have a relationship with control over the retrieval of episodic memories.

A large number of studies have found that decreased hippocampal volume is associated with poorer recall of episodic information, including both spatial and verbal material. This association is observed across a number of clinical populations or groups in whom decreased hippocampal volume is notable as compared to control individuals, including nondemented older adults (Zimmerman et al., 2008), and individuals with Alzheimer's disease (Kuczynski et al., 2008), subjective memory deficit (SMD)(Stewart et al., 2008), schizophrenia (Cannon et al., 2005), and developmental amnesia (DA)(Adlam et al., 2005), among others.

Conversely, increases in hippocampal volume have been associated with better spatial memory in animals and humans (Jacobs et al., 1990; Sherry et al., 1993; Biegler et al., 2001), most notably in London taxi-drivers who show increased hippocampal volume, as compared to control individuals (Maguire et al., 2000). These studies suggest that superior spatial ability or an increased dependence on spatial learning is correlated with increases in hippocampal volume. Although these studies focus on spatial memory, evidence suggests that spatial memory is but one type of episodic memory that relies on the hippocampus (Burgess et al., 2002). Taken together, the previous evidence suggests a relationship between hippocampal volume and episodic memory retrieval.

What is less understood is whether hippocampal volume also effects the degree to which one can control access to episodic memories, either to enhance their retrieval or, alternatively, to stop their retrieval. Recent neuroimaging studies have suggested that by exerting inhibitory control over the hippocampus, lateral prefrontal cortex (LPFC) may play a role in inhibiting the retrieval of episodic memories [e.g., the Think/No-Think task (TNT); (Anderson et al., 2004; Depue et al., 2007). More specifically, increased acti-

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Additional Supporting Information may be found in the online version of this article.

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vation in regions of the LPFC [e.g., middle frontal gyrus (MFG)] is correlated with decreased activity in the hippocampus across individuals (Anderson et al., 2004; Depue et al., 2007) and within individuals across time (Depue et al., 2010). Furthermore, across individuals, an increased ability to inhibit memory retrieval (as indicated by reduced behavioral recall) predicts decreased activation of the hippocampus, while not surprisingly, increased enhancement of retrieval (as indicated by increased behavioral recall) is correlated with increased activation of the hippocampus (Depue et al., 2007).

In consideration of these findings, the goal of the current study is to investigate how individual differences in hippocampal volume are related to the ability to control memory retrieval, as assessed by the Think/No-Think (TNT) task (Anderson and Green, 2001). To do so, we examined anatomical and behavioral data taken from the study of Depue et al. (2007) in which sixteen English-speaking adults ($N = 6$ women) from 19 to 29 years of age performed the T/NT task (Anderson and Green, 2001) while brain activation was recorded using fMRI (for behavioral and imaging methodology see Depue et al., 2007).

For purposes of this report, anatomical imaging data was segmented into subcortical regions, using FSL's FMRIB Integrated Registration and Segmentation Tool (FIRST; FSL v4.0.1, http://www.fmrib.ox.ac.uk/fsl/first/index.html), which is a model-based segmentation tool that allows for parcellation of several subcortical brain structures from high resolution T1-weighted images of the brain (Patenaude, 2007; Patenaude et al., 2007, 2008). Importantly, this tool enables an unbiased approach to segmentation of the regions, which are notoriously hard to manually trace due to their small structure size.

Automated segmentation of amygdala and hippocampus was performed using FIRST (FSL v4.0.1) which uses a Bayesian probabilistic approach. The shape and appearance models in FIRST are constructed from a library of manually segmented images. The manually generated labels are parameterized as surface meshes and then modeled as a point distribution. Using the learned models, FIRST searches through shape deformations that are linear combinations of the modes of variation to find the most probable shape instance given the observed intensities from the input image. Using T1 images, the segmentation was performed with two-stage affine transformation to standard space of MNI 152 at 1-mm resolution (Morey et al., 2009; Woolrich et al., 2009). The first stage utilized a standard 12° of freedom registration to the template and the second stage applied 12° of freedom registration using an MNI152 subcortical mask to exclude voxels outside the subcortical regions. Boundary voxels were thresholded at $z = 2$ and $z = 3$, along with the recommended number of modes (iterations) for the hippocampus (30) and amygdala (50). All segmentations were then visually inspected to assess boundaries by two independent raters for each of the two boundary thresholded training sets ($z = 2$, $z = 3$). Because $z = 2$ yielded a more conservative boundary threshold that included the hippocampus proper, while minimizing neocortical tissue, this data set was selected for final analyses.

TABLE 1.

Correlations Between Trial Conditions, (a) Think Index (T-Base; Think Trials Minus Baseline Trials), (b) Baseline Trials (Base), and (c) No-Think Index (NT-Base; No-Think Trials Minus Baseline Trials) and Volume (mm^3) of the Bilateral Hippocampus (L-Hip, R-Hip) and Amygdala (LAmy, R-Amy)

	L_Hip	L_Amy	R_Hip	R_Amy
a) T-Base	−0.43+	0.01	−0.73*	0.01
b) Base	0.17	−0.14	0.10	−0.24
c) NT-Base	0.55*	0.14	0.53*	0.09

Significant or trends towards significant correlations are shown in green for Think index and red for No-Think index. + = trend towards significance, * = significant correlation, Bonferroni corrected with mean level of correlation.

As reported previously (Depue et al. 2007), behavioral results from the testing phase of the T/NT task for 16 participants showed that, after the 12 repetitions of cues, recall significantly differed for T and NT items [$t(15) = -4.29$, $P < 0.006$; Fig. 1]. Furthermore, there was a strong trend towards significance for recall to improve during the T condition compared to baseline [$t(15) = 1.49$, $P = 0.07$]. Conversely, in the NT condition, there was a significant reduction in the ability to remember the items relative to baseline [$t(15) = -2.28$, $P = 0.02$].

To examine the correlation between hippocampal volume and control over memory retrieval, two indices were created for each participant. The first, assessing the ability to inhibit memory retrieval, was calculated as the percentage recall on No-Think (NT) trials minus the percentage recall from baseline trials. Hence, the smaller the value of this No-Think index, the greater ability to inhibit retrieval. The second, assessing the ability to enhance memory retrieval, was calculated as the percentage recall on Think (T) trials minus the percentage recall from baseline trials. Hence, the larger the value of this Think index, the greater ability to enhance retrieval. In addition, recall on baseline trials, which neither get inhibited nor enhanced, was also considered. These three behavioral values then were correlated with the volume provided by FIRST for the bilateral hippocampus accounting for whole brain volume removed by regression. Results suggest that significant decreases in the left and right hippocampal volume were related to an increased ability to inhibit memory retrieval ($df = 14$, L-Hip, $r = 0.57$, $P = 0.023$, R-Hip, $r = 0.53$, $P = 0.04$) (see Table 1; Figs. 2A,B,E,F). Similarly, a trend towards significant decrease in the left and a significant decrease in the right hippocampal volume were related to an increased ability to enhance memory retrieval ($df = 14$, L-Hip, $r = –0.43$, $P = 0.096$, R-Hip, $r = –0.73$, $P = 0.0013$) (see Table 1; Figs. 2A,B,E,F). Baseline levels of recall had no significant relationship with bilateral hippocampal volume (see Table 1; Supporting Information:S1). Also, as a means of controlling for other factors that may be associated with hippocampal volume we examined the correlation with age after accounting for whole brain volume ($df = 14$, L-Hip, $r = –0.04$, $P > 0.05$, R-Hip, $r = –0.02$, $P > 0.05$), as such

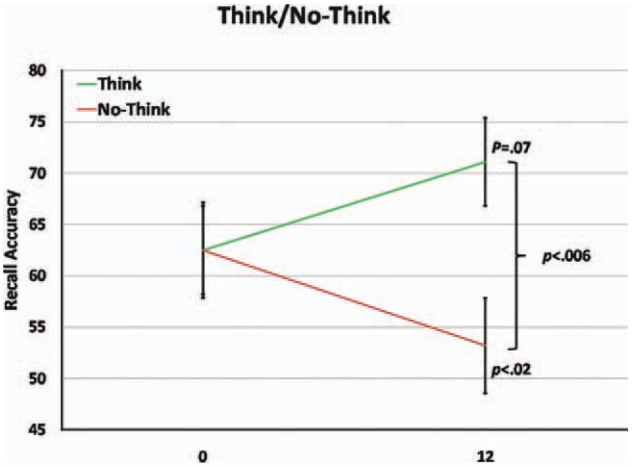

FIGURE 1. Behavioral results for the TNT (Depue et al., 2007). Percentage recall for Think (T) trials is shown in green, and recall for No-Think (NT) trials is shown in red. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

regressing out age had no impact on the overall correlations with hippocampal volume and the three behavioral measures of memory. Similarly, we conducted *t*-tests and correlations to examine the relationship of gender and hippocampal volume accounting for whole brain volume [L-Hip; $t(14) = -0.408$, $P = 0.69$; $r = 0.008$, $P > 0.05$; R-Hip; $t(14) = -0.593$, $P = 0.56$, $r = 0.01$, $P > 0.05$], results suggest that gender did not significantly affect hippocampal volume or its association with memory performance. While hippocampal volumes varied among participants (L-Hip, $M = 6{,}348$ mm^3, SD = 789; R-Hip, $M = 6{,}393$ mm^3, SD = 881), there appears to be a great deal of variability in the volume of this structure. Our analyses of meta-analytic results show that the actual volume calculations of the hippocampus vary to a high degree (900–8,900 mm^3) dependent on the populations under investigation, as well as, the methodology used to account for estimation and whole brain volume (i.e., hippocampal volume divided by whole brain volume, hippocampal volume regressed out of correlations, and/or whether any neocortex is included in the analyses, etc.)(Van Petten, 2004; Woon et al., 2010). Although overall estimates vary to a high degree, it appears as though the percentage of a standard deviation (SD) compared with total hippocampal volume estimate remains relatively stable across studies. Therefore, we suggest as a rough estimate that a single SD appears to constitute 10–15% mm^3 of overall hippocampal volume (Videbach and Ravnkilde, 2004; Smith, 2005; Morey et al., 2009; Woon et al., 2010). To examine whether these relationships are specific to the hippocampus, we assessed whether volume of the amygdala was correlated with the three

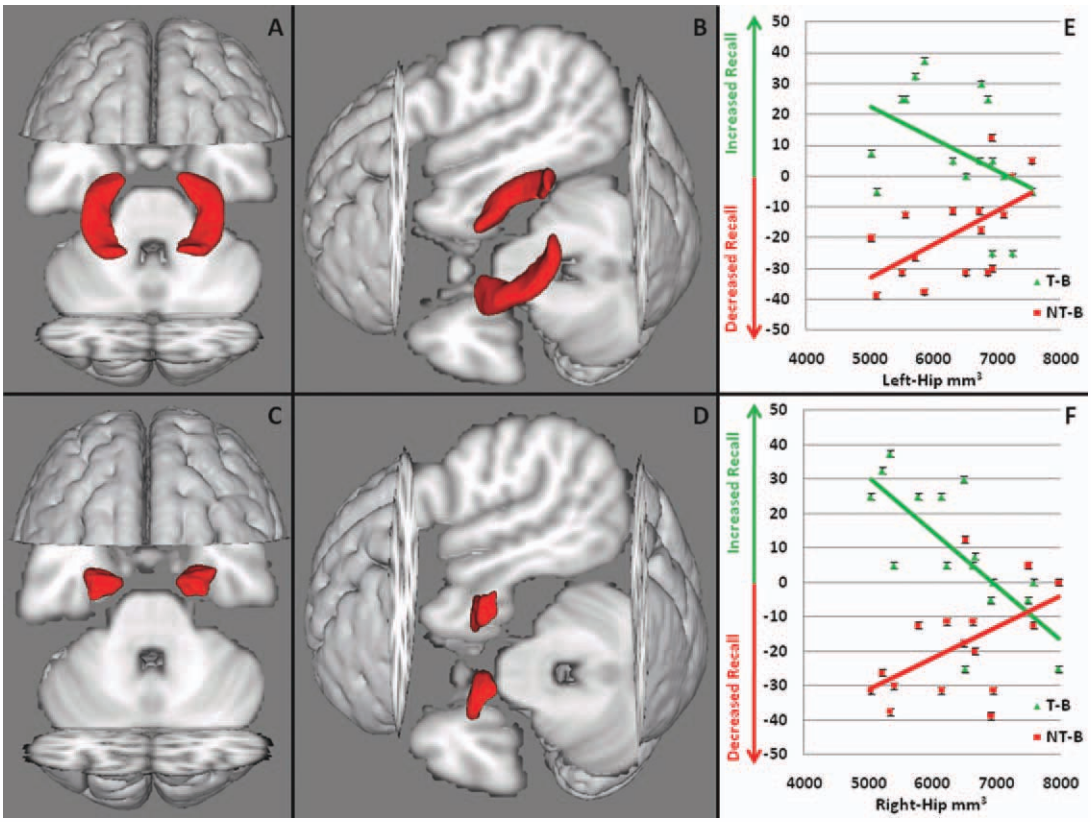

FIGURE 2. A, B: Segmented bilateral hippocampus. C, D: Segmented bilateral amygdala. E, F: Regression scatter plots of left and right hippocampal volume (mm^3) and change in recall from baseline for the Think index (T-B; Think minus baseline trials; green) and No-Think index (NT-B; No-Think minus baseline trials; red) for each individual. Error bars represent standard error. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

behavioral values previously described. We chose the amygdala as a control region based on the fact that we previously found it to be activated during the inhibition of emotional memory retrieval, although individual differences in activity had no relationship with the behavioral success of inhibition of memory retrieval (Depue et al., 2007). These results yielded no significant correlations (see Table 1; Figs. 2C,D; Supporting Information S1).

Importantly, these analyses suggest that better inhibition, as well as, better enhancement of memory retrieval are predicted by smaller bilateral hippocampal volume. This relationship appears to be specific for control over memory retrieval mechanisms, as hippocampal volume showed no relationship to baseline recall. Also suggesting specificity of the effect, similar relationships between control over memory retrieval and volume were not observed for the amygdala.

In our prior work, we also found that increased activity of the rMFG across individuals and across time correlates with decreased activity of the hippocampus bilaterally (Depue et al., 2007, 2010). Furthermore, increases in activity in the rMFG as well as decreases in activity of the bilateral hippocampus predicted increased behavioral inhibition of memory retrieval (see Supporting Information Depue et al., 2007, 2010). Therefore, to assess whether putative control of the rMFG over the bilateral hippocampus during No-Think trials is related to anatomy, we examined whether correlated activity between these regions is related to bilateral hippocampal volume. To do so, for each individual we determined the correlation of activity between the rMFG and bilateral hippocampus over the time course of all NT trials during the experimental phase. This correlation was then transformed to a Z score and correlated with an individual's bilateral hippocampal volume. These results yielded significant correlations for the left and right hippocampus ($df = 14$, L-Hip, $r = 0.51$, $P = 0.04$, R-Hip, $r = 0.50$, $P = 0.05$; Supporting Information S1), perhaps suggesting that PFC communication with, or modulation of, the hippocampus may be related to its volume. While there was a distinct relationship with correlated activity between brain regions (rMFG-Hip) during No-Think trials, during Think trials no such relationship was observed between prefrontal regions and hippocampal activity. Thus, similar analyses were not possible for Think trials.

The current study suggests that the anatomy of the hippocampus may be related to an individual's ability to exert cognitive control over memory retrieval. During NT trials in which an individual was asked to inhibit memory retrieval, reduced volume of the bilateral hippocampus was related to reductions in recall memory. Similarly, during T trials in which individuals were asked to enhance memory retrieval reductions in hippocampal volume were also found to predict behavior by increased recall memory (a trend towards significance for the left hippocampus and a significant effect for the right hippocampus). In contrast, hippocampal volume did not predict recall for baseline trials, on which individuals did not attempt to exert control over the memory. Importantly, these relationships suggest that hippocampal volume appears to specifically affect inhibition and enhancement of memory retrieval, but not initial learning. The lack of an association between amygdalar volume and the ability to either inhibit or enhance retrieval of a memory, suggests the effect maybe specific to the hippocampus.

Moreover, the correlation in activity during NT trials between the bilateral hippocampus and the rMFG, the putative area exerting cognitive control over the hippocampus, appears to be related to the volume of the bilateral hippocampus. Specifically, greater correlated activity, as indicated by increased activity of rMFG coinciding with decreased activity of the bilateral hippocampus over time during NT trials, was related to decreases in bilateral hippocampal volume. We speculate that the ability of the rMFG to communicate with, or modulate activity of, the hippocampus may depend, in part, on this region's anatomy.

While our findings are preliminary and will require replication, there is much literature supporting the possibility that the communication or modulation of hippocampal activity by the LPFC influences recall, most notably as illustrated in the subsequent memory effect literature (Wagner et al., 1998, 2002). These studies reveal that increased activation in areas of LPFC predicts both the success of encoding a stimulus target and also whether the target is subsequently retrieved. Anatomically, such control could be exerted via anatomical connections between regions 9/46 (MFG) and the hippocampus/entorhinal cortex (EC) (Goldman-Rakic and Rosvold, 1970; Petrides and Pandya, 2007).

What is less clear is the relation between hippocampal volume and cognitive control. In the current study, both increased enhancement and inhibition of memory retrieval were correlated with decreased hippocampal volume. This finding raises the possibility that magnitude of prefrontal modulation of the hippocampus is related to functional attributes associated with volume. Indeed, variation in gray matter volume has been positively associated with both growth (size and number) and activity level (cortical evoked potentials) of neurons (May and Gaser, 2006; May et al., 2007), as well as with fMRI activation (Ilg et al., 2008). While there is little evidence on the relation between cognitive control and volume of the region under control, we speculate that aspects of regional volume (e.g., gray matter) may influence either basal or stimulus-induced neural activity as indicated in the above studies. That is, one or both of these neural properties may influence the degree to which cognitive control over a region is exerted. For instance, a hippocampus that exhibits decreased volume, and thus decreased basal and/or stimulus-induced activity, may require reduced or less enduring cognitive control in order to achieve modulation over memory retrieval.

In sum, this study provides evidence that the anatomy of the hippocampus is related to an individual's behavioral ability to control memory retrieval. Furthermore, the amount of cognitive control, which maybe dependent on LPFC communication with, or modulation of, the hippocampus may also be related to anatomy. Specifically, increased cognitive control over memory processes appears to be related to decreases in hippocampal volume.

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