Neuropsychologia 49 (2011) 3795–3800

Contents lists available at SciVerse ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

Structural correlates of prospective memory

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ARTICLE INFO

Article history:
Received 18 May 2011
Received in revised form
20 September 2011
Accepted 23 September 2011
Available online 1 October 2011

Keywords:
Prefrontal cortex
Hippocampus
Structural MRI
Aging
Episodic memory

ABSTRACT

Prospective memory (PM) includes the encoding and maintenance of an intention, and the retrieval and execution of this intention at the proper moment in the future. The present study expands upon previous behavioral, electrophysiological, and functional work by examining the association between grey matter volume and PM. Estimates of grey matter volume in theoretically relevant regions of interest (prefrontal, parietal, and medial temporal) were obtained in conjunction with performance on two PM tasks in a sample of 39 cognitively normal and very mildly demented older adults. The first PM task, termed focal in the literature, is supported by spontaneous retrieval of the PM intention whereas the second, termed non-focal, relies on strategic monitoring processes for successful intention retrieval. A positive relationship was observed between medial temporal volume and accuracy on the focal PM task. An examination of medial temporal lobe subregions revealed that this relationship was strongest for the hippocampus, which is considered to support spontaneous memory retrieval. There were no significant structure–behavior associations for the non-focal PM task. These novel results confirm a relationship between behavior and underlying brain structure proposed by the multiprocess theory of PM, and extend findings on cognitive correlates of medial temporal lobe integrity.

1. Introduction

Prospective memory (PM) refers to the process of remembering to remember. PM requires the initial planning and formation of an intention, later recognition of a cue and recollection of its associated intention, and executing this intention in coordination with ongoing activity (Marsh, Hicks, & Watson, 2002). PM is fundamental to the performance of every-day tasks such as remembering to turn off one's cell phone in a movie theatre or remembering to stop for groceries on the way home from work. In typical event-based PM paradigms (i.e., responding to a specific event in the future), participants engage in a primary ongoing task while simultaneously remembering to make a unique response to infrequent targets associated with a previously encoded intention (McDaniel & Einstein, 2007).

According to the multiprocess theory (McDaniel & Einstein, 2000, 2007), qualitatively different processes support the retrieval of the PM intention depending upon the context. A determining factor is the degree to which encoded features of the PM cue are extracted as part of the ongoing activity (see Einstein et al., 2005; McDaniel & Einstein, 2007). For *non-focal* tasks, ongoing task processing does not stimulate processing of critical PM cue features (see Knight et al., 2011; McDaniel & Einstein, 2007). For example, when the PM cue is a particular syllable (e.g., "tor"), and the ongoing activity requires a category judgment (e.g., is "tornado" a member of given category "weather"), the ongoing task emphasizes semantic features, whereas the critical recognition features for the PM cue are syllabic. This lack of overlap requires additional strategic monitoring processes for successful non-focal PM cue recognition (Einstein et al., 2005; see Shallice & Burgess, 1991, and Smith, 2003 for views of PM monitoring).

For *focal* tasks, information relevant to the ongoing task overlaps with encoded PM cue features. In the just mentioned category-decision activity, the whole-word target "tornado" would be a focal cue, assuming people access semantic features during intention formation and when making category decisions. From the multiprocess theory perspective, such focal cues elicit spontaneous retrieval processes to support PM (see Einstein & McDaniel, 1996; McDaniel, Robinson-Riegler, & Einstein, 1998, for initial characterizations of spontaneous PM retrieval).

The predictions of the multiprocess theory were examined in a seminal study conducted by Einstein et al. (2005; see also Scullin, McDaniel, Shelton, & Lee, 2010) that manipulated cue focality. Participants demonstrated significant slowing when a non-focal PM demand was embedded in an ongoing task (relative to a control condition that involved only the ongoing task), but no such costs were observed when a focal PM demand was embedded. The ongoing task costs in the non-focal condition were directly associated

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doi:10.1016/j.neuropsychologia.2011.09.035

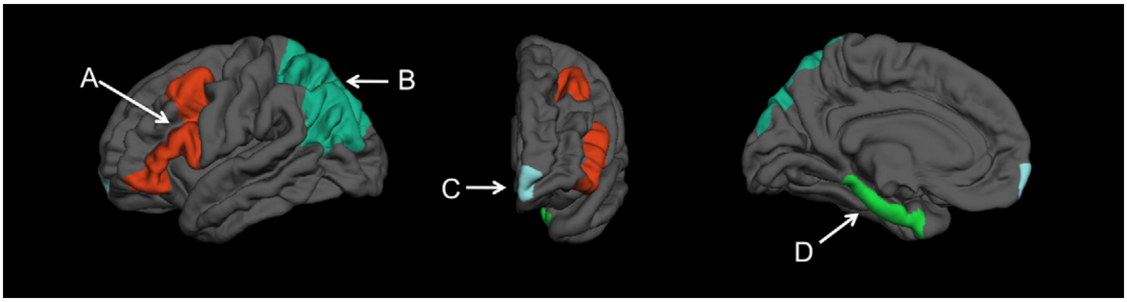

Fig. 1. Example of ROIs displayed on the template brain from Freesurfer. (A) Ventral/dorso-lateral prefrontal cortex; (B) lateral parietal cortex; (C) anterior prefrontal cortex; (D) medial temporal lobe.

with PM cue detection and declined over time during the task. The authors interpreted the ongoing task costs observed in the non-focal condition, and their decline over time, as evidence for an underlying, strategic monitoring process. The lack of ongoing task costs in the focal condition, accompanied by high PM performance, suggested a more reflexive, spontaneous retrieval process supporting PM without the need for an attention-demanding monitoring process. The critical point for the present study is that the multiprocess theory anticipates engagement of two brain networks, one tied to effortful modulations of attention, and another for spontaneous retrieval. Moreover, the relative importance of these networks to PM is dependent on the relative non-focal or focal nature of the task (McDaniel & Einstein, 2007, 2011).

An expanding interest in PM has encouraged investigation of its neural underpinnings (e.g., Burgess, Gonen-Yaacovi, & Volle, 2011; Martin et al., 2007; McDaniel & Einstein, 2011; West, 2011). Using PET and fMRI, researchers have found consistent activation of several brain regions when examining event-related PM; most prominent among these is an anterior prefrontal region located approximately in Brodmann area 10 (BA 10; Burgess, Quayle, & Frith, 2001, 2011; Reynolds, West, & Braver, 2009). As the vast majority of this work utilizes non-focal tasks, this region is likely an integral node in the network supporting effortful attentional processes needed for non-focal PM (Simons, Scholvinck, Gilbert, Frith, & Burgess, 2006). Although much focus has been on anterior prefrontal cortex, PM success has also been linked to parietal (Burgess et al., 2011, 2001; Martin et al., 2007; Reynolds et al., 2009), and medial temporal lobe (MTL, see Burgess, Maguire, & O'Keefe, 2002 for a review) regions. Additionally, as a mainstay of cognitive control, the lateral parietal and dorsolateral prefrontal regions of the dorsal attentional network (Corbetta & Shulman, 2002) are other potential loci facilitating non-focal performance.

For a network supporting spontaneous retrieval of PM intentions, there is a strong basis to examine the MTL. Functional activations in the hippocampus are tied to spatial, episodic, and recognition memory (Burgess et al., 2002; Eichenbaum, Yonelinas, & Ranganath, 2007), and even focal PM performance in a naturalistic setting (Kalpouzos, Eriksson, Sjolie, Molin, & Nyberg, 2010). Similarly, the volumes of MTL structures, in particular the hippocampus, have been linked to episodic (e.g., Head, Rodrigue, Kennedy, & Raz, 2008) and spatial memory (e.g., Erickson et al., 2009). The importance of the hippocampus for relational memory (Eichenbaum & Cohen, 2001; Konkel & Cohen, 2009) along with its automaticity of function (Konkel & Cohen, 2009; Moscovitch, 1994), suggest that it may be crucial for the demands of a focal PM task (see McDaniel & Einstein, 2007; McDaniel et al., 1999). Although the hippocampus has a strong role in recollection, its surrounding structures may be integral for different aspects of memory (Aggleton & Brown, 2006; Ranganath et al., 2004). As such, the MTL subregions may be differentially important for PM.

The behavioral and functional studies to date suggest several mechanisms and brain regions important for successful performance of PM. To the authors' knowledge, only studies of neurological patients (e.g., Groot, Wilson, Evans, & Watson, 2002; Mathias & Mansfield, 2005) have looked at the link between brain structure and performance on PM tasks, and no studies have examined how these relationships differ depending on type of PM task (i.e., non-focal vs. focal). Here we examine relationships between focal and non-focal PM performance and grey matter volume in four regions-of-interest (ROIs) in a convenience sample of cognitively normal and very mildly demented older adults. We predicted that focal performance would be selectively associated with the MTL, with the strongest relationship with the hippocampus proper, whereas prefrontal and parietal region volumes would be especially associated with non-focal performance.

2. Materials and methods

2.1. Participants

Participants were a subsample of community-dwelling older adults from a larger study examining PM performance, aging and dementia (McDaniel et al., 2011). Participants were recruited from the Knight Alzheimer's Disease Research Center at Washington University and screened for neurological illness (e.g., Parkinson's, Huntington's, seizures, major head injury). Participants were classified as cognitively normal (CDR = 0; n = 21 (16 female)) or very mildly demented (CDR = 0.5; n = 18 (12 female)) based on the Clinical Dementia Rating scale (CDR; Morris, 1993). A health composite score was created based on the absence or presence (coded 0 or 1) of hypertension, diabetes, history of heart problems (i.e., atrial fibrillation, angioplasty, bypass surgery, congestive heart failure, or pacemaker implantation), history of stroke or transient ischemic attack, history of depression, and mild head injury. The resulting value between 0 and 6 captures multiple health factors into a general measure of overall health, while reducing the need for multiple covariates (reducing power) in the relatively small sample. Demographics characterizing the sample are presented in Table 1.

2.2. Behavioral task

Participants were engaged in an ongoing category-judgment task where they decided whether an exemplar word was a member of a specified category (e.g., green COLOR; see Einstein et al., 2005). The exemplar word was always presented in lowercase letters on the left, and the category was always simultaneously displayed in uppercase letters on the right. Three counterbalanced blocks of 106 word-category pairings were presented, with a category match on half of the trials. Two of these blocks had an additional embedded PM task; the third was a control block with only the ongoing category judgment task. For the focal PM block, participants were instructed to press "Q" whenever they saw a particular word (either "tortoise", "raspberry", or "aluminum"). For the non-focal PM block, participants were instructed to press "Q" if they ever saw a word containing a particular syllable (either 'tor', 'ras', or 'min'). The PM targets always occurred in the exemplar rather than the category word and the PM targets always appeared on trials 31, 72, and 102 of both the focal and non-focal blocks. For each PM block, the PM cue was presented three times, increasing total trials in these blocks to 109 trials. The low number of PM trials is intended to maintain the design as a true PM task rather than creating a vigilance task, and as such, is intended to capture PM processes similar to everyday life. Because the same PM target word was repeated three times in the focal condition, non-target words were also repeated to remove any distinctiveness that might arise from this repetition (cf. McDaniel & Einstein, 1993). Eleven non-targets were

Table 1
Demographic and behavioral data.

$N=39$	Mean (SD)	Range
Age (years)	78.1 (7.8)	62–94
Education (years)	14.7 (3.0)	10–20
Health composite[a]	1.3 (1.2)	0–4
MMSE	28.2 (1.9)	24–30
SRT free recall	23.8 (10.6)	4–10
Digit span	11.5 (2.3)	6–15
Digit symbol	41.3 (12.7)	14–67
Trail making A	40.2 (15.4)	19–83
Trail making B	100.7 (42.1)	34–180
Boston naming test	55.0 (5.5)	34–60
Ongoing task RT (s)		
Control block	1722(453)	994–2976
Focal block	1737(407)	1165–2958
Non-focal block	1951(670)	1026–3494
Accuracy (%)		
Ongoing task	.95 (.02)	.90–.98
Focal PM	.68 (.47)	0–1.0
Non-focal PM	.29 (.42)	0–1.0

RT—reaction time in seconds; MMSE—Mini-Mental Status Exam (Folstein, Folstein, & McHugh, 1975); SRT—Free and Cued Selective Reminding Test (Grober, Buschke, Crystal, Bang, & Dresner, 1988); Digit Span—sum of digit span backward and forward (Wechsler, 1987); Boston Naming Test (Mack, Freed, Williams, & Henderson, 1992); Digit Symbol and Trail Making A and B (Wechsler, 1987).

[a] Health composite incidence rates: diabetes (5), hypertension (22), stroke (5), heart problems (14), depression (4) and mild head injury (4). Co-morbidity possible.

repeated 3 times and 9 were presented 2 times. The behavioral procedure is also described in McDaniel et al. (2011).

2.3. Imaging protocol

The majority of images ($n=30$) were collected on a Siemens 1.5 Tesla Vision scanner (Erlangen, Germany). Two-to-four T1-weighted saggital MP-RAGE scans (TR = 9.7 ms, TE = 4 ms, flip angle = 10°, TI = 20 ms, 1 mm × 1 mm × 1.25 mm resolution) were acquired for each subject. Data for a subset of individuals ($n=9$) were acquired on a Siemens 3 Tesla Trio scanner. Two T1-weighted saggital MP-RAGE scans (TR = 2400 ms, TE = 3.08 ms, flip angle = 8°, TI = 1000 ms, 1 mm × 1 mm × 1 mm resolution) were acquired for these participants. Multiple scans for an individual were aligned using a rigid body transform and averaged together. There were on average 20.0 months (SD = 18.4) between scan acquisition and behavioral testing.

2.4. Image analysis

Regional grey matter volume estimates were obtained using the Freesurfer image analysis suite, which implements an automated labeling procedure (Desikan et al., 2006; Fischl et al., 2004) in which each voxel in an MR image is assigned a neuroanatomical label based on probabilistic information from a manually labeled training set. This procedure is highly robust and generates anatomical labeling and regional volume estimates with a high correspondence to those obtained with manually generated labels (Fischl et al., 2004).

Regions-of-interest (ROIs) were obtained from the Desikan–Killiany atlas (Desikan et al., 2006) included as the default cortical parcellation within Freesurfer. Using the available anatomical delineations present within this atlas, ROIs were selected to approximate brain regions implicated by both neuropsychological (e.g., Groot et al., 2002; Mathias & Mansfield, 2005; McDaniel & Einstein, 2011) and neuroimaging studies of prospective memory (e.g., Burgess et al., 2011; Reynolds et al., 2009; West, 2011). These ROIs were anterior prefrontal cortex (APFC, within BA 10), ventral/dorsal-lateral prefrontal cortex (VL/DLPFC; combined caudal middle frontal gyrus and inferior frontal gyrus), lateral parietal cortex (combined superior and inferior parietal cortex) and medial temporal lobe (MTL; combined parahippocampal gyrus, entorhinal cortex, and hippocampus) (see Fig. 1 and Desikan et al., 2006 for details on anatomical boundaries). Volumes were adjusted for total intracranial volume using a covariance approach (Buckner et al., 2004) and summed across hemispheres as no *a priori* effects of hemisphere were expected.

2.5. Statistical analyses

Partial correlations were computed between each ROI (VL/DLPFC, MTL, parietal cortex, APFC) and accuracy on the focal and non-focal PM tasks. Potential confounding variables with even marginal zero-order correlations ($p < .25$) with behavior or brain volumes were considered as covariates. Partial correlations controlled for gender, age, CDR status, education, scanner type, and a health-composite. Because our primary interest was in behavior–structure associations, age and CDR status were treated as nuisance covariates. Additional partial correlations were conducted to examine the relationship between the volume of the MTL subregions and focal PM accuracy with the same covariates. Alpha was set at .05. As we had *a priori* directional hypotheses, all p-values refer to one-tailed tests.

Table 2
Partial correlations between volume and behavioral performance.

Region	Focal PM	Non-focal PM
Parietal	−.007	.066
VL/DLPFC	.016	.005
Anterior PFC	.306*	−.011
MTL	.473**	.282+

* $p < .05$.
** $p < .01$.
\+ $p < .1$.

3. Results

3.1. Behavioral task

Behavioral data are presented in Table 1 (cf. larger sample of McDaniel et al., 2011). Ongoing category-judgment accuracy was high ($M=.95$, SD = .02), and did not vary across the three blocks ($F_{(2,76)}=.064$, $p=.94$). RT for the ongoing category-judgment task did significantly vary across the three blocks ($F_{(2,72)}=9.63$, $p<.01$).[1] Pairwise comparisons indicated that the category-judgment responses in the non-focal block were significantly slower than those in both the focal ($p=.003$) and control ($p=.002$) blocks, suggesting that strategic monitoring processes were supporting retrieval in the non-focal block. Most importantly, participants were significantly more accurate in remembering to respond to the appropriate cue in the focal PM ($M=.65$, SD = .46) than the non-focal PM ($M=.29$, SD = .41) task ($t_{(40)}=4.01$, $p<.001$), replicating previous work demonstrating better performance on focal than non-focal tasks (Einstein et al., 2005; Scullin et al., 2010). Due to the low number of trials in the design and overall low accuracy, RT for PM trials could not be reliably estimated.

3.2. Behavior–structure correlations

The partial correlations between structure and PM accuracy are presented in Table 2. For the non-focal PM task, there were no significant relationships between any of the ROIs and accuracy. For the focal PM task, neither parietal nor VL/DLPFC volumes were associated with accuracy. Post hoc analyses dividing the parietal cortex into superior and inferior regions, and the VL/DLPFC into caudal middle frontal gyrus and inferior frontal gyrus did not yield any significant correlations with focal or non-focal PM accuracy. As expected, the volume of the MTL was significantly correlated with focal PM accuracy (partial $r_{(31)}=.473$, $p<.01$). In addition, there was a significant association between APFC volume and focal PM accuracy (partial $r_{(31)}=.306$, $p<.05$). As suggested by the scatter plot in Fig. 2, the association between APFC and focal performance is highly influenced by one individual. This was confirmed by analyses of outlier statistics (e.g., Cook's distance). Removing this individual from the analysis greatly reduced the association between focal PM accuracy and APFC (partial $r=.218$, $p=.115$). The relationship between MTL volume and focal performance cannot, however, be explained by the influence of outlier points (Table 3).

Because of the theoretical significance of particular MTL subregions to memory, we examined the associations between focal PM performance and these regions. For the focal PM task, hippocampal volume (partial $r_{(31)}=.576$, $p<.001$) was significantly correlated

[1] Two subjects were eliminated from the RT analysis, one for measurement error and one determined to be an outlier as it was more than 3 standard deviations away from the group mean.

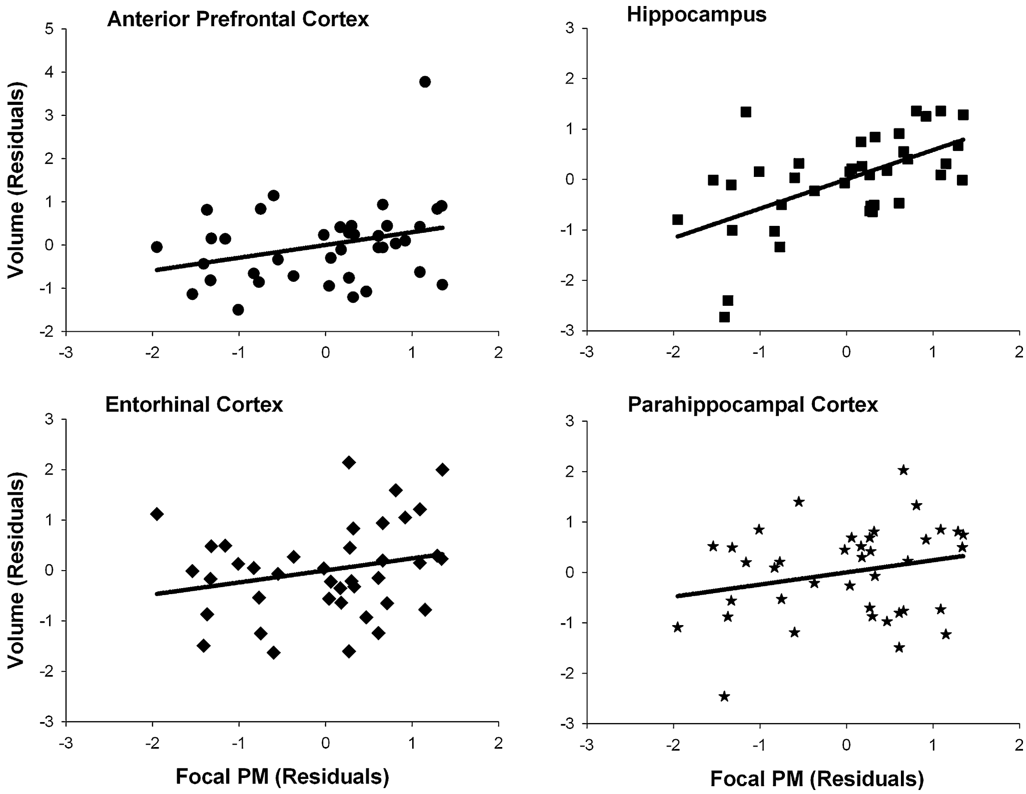

Fig. 2. Scatter plots of associations between focal performance and regional brain volumes.

Table 3
Distribution of prospective memory behavioral data.

Task	0 correct	1 correct	2 correct	3 correct
Focal	30.8%	2.6%	7.7%	59.0%
Non-focal	61.5%	10.3%	7.7%	20.5%

with PM accuracy, but the relationship between entorhinal (partial $r_{(31)} = .230$, $p = .098$) and parahippocampal volume (partial $r_{(31)} = .228$, $p = .101$) and focal PM accuracy fell short of significance (Fig. 2). Examination of the relative strength of associations between volume and PM accuracy across regions (Steiger, 1980) revealed that the *a priori* theorized association between hippocampal volume and focal PM accuracy was significantly stronger than that for parahippocampal ($Z = 2.42$, $p < .01$), entorhinal ($Z = 2.34$, $p < .01$), or APFC cortices ($Z = 1.72$, $p < .05$).

4. Discussion

The goal of the current study was to examine a previously unexplored link between focal and non-focal PM performance and regional brain volume. We demonstrated a strong relationship between MTL integrity and performance on a focal PM task independent of age and cognitive status, a relationship that was not evident for non-focal PM performance. We then decomposed MTL into three subregions and examined the relationships between these regions and focal PM performance. Significant positive correlations were observed for hippocampal and parahippocampal volumes, with comparisons of correlations confirming that the strongest correlation was with hippocampus proper. These findings are theoretically significant as they support the predictions of the multiprocess theory that retrieval in a focal PM task is subserved by the hippocampus (McDaniel & Einstein, 2007).

The current findings extend previous research linking MTL volume to episodic (e.g., Head et al., 2008) and spatial (e.g., Erickson et al., 2009) memory. The relative contributions of the hippocampus and surrounding structures to memory, more generally, have been explained in several ways. A popular dissociation between the two is between recollection and familiarity. In numerous fMRI studies, activation in the hippocampus is associated with memories recalled by individuals, or that have a high level of specific detail. In contrast, activations in the surrounding cortices are associated with feelings of familiarity without the depth of specific details (e.g., Aggleton & Brown, 2006; Ranganath et al., 2004). The dissociations observed within the MTL in the present study could be due to a reliance on PM cue recollection rather than a signal of familiarity to support focal PM performance, although familiarity may still contribute to cue recognition in a lesser manner.

This dependence on recollective memory comes from the associative nature of PM. During intention formation, a connection is made between the PM cue and the intended response. During focal PM tasks, the ongoing activity stimulates processing of features congruent with those encoded during intention formation, triggering spontaneous retrieval of the associated response. The hippocampus has been proposed as a structure uniquely critical for such associative memory formation and retrieval (Eichenbaum & Cohen, 2001; Konkel & Cohen, 2009; Moscovitch, 1994). Therefore, it is the relational nature of the hippocampus that makes it important both for the recollection of episodic memories and thus for PM memory. Once focal PM intentions are retrieved, prefrontal executive systems might become involved in coordinating execution of the PM response alongside performance of the ongoing task (McDaniel & Einstein, 2011; McDaniel et al., 1999). Consistent with this interpretation is the observed association between focal PM and APFC volume, although the lack of robustness of this effect warrants further study.

In non-focal PM tasks, PM features are not wholly congruent with those of the ongoing activity and thus unlikely to trigger spontaneous retrieval of the associated response (cf. Moscovitch, 1994). Consequently, detecting and responding to non-focal PM cues requires additional strategic monitoring processes (McDaniel & Einstein, 2000, 2007) typically associated with prefrontal regions as seen in the fMRI work with non-focal tasks (Burgess et al., 2011, 2001; Reynolds et al., 2009). Additionally, it was expected that dorsal attentional areas in parietal and VL/DLPFC regions would be integral to non-focal performance; however, no significant relationships were observed. Note that previous work has found equivalent reliability across relatively focal and non-focal PM tasks (Rose, Rendell, McDaniel, Aberle, & Kliegel, 2010, albeit within another PM paradigm); accordingly, it seems unlikely that lower reliability for the non-focal task relative to the focal task was responsible for the non-focal results. It is more likely that the overall poor behavioral performance on the non-focal task limited possible detection of any relationship between volume and non-focal PM accuracy. Further, the low number of PM target trials prevented a reliable estimate of RT for use as a dependent measure. Future investigations using easier non-focal tasks would eliminate floor effects and increase the sensitivity and power of the design. Such a change would provide a more robust examination of PM performance and additionally allow investigations into structural relationships with both accuracy and reaction time.

In addition to low non-focal performance, there are other limitations of our study. The fMRI literature with PM has implicated medial temporal, parietal, and prefrontal regions of the brain (Burgess et al., 2011; Reynolds et al., 2009). These functional activations, however, do not perfectly correspond to any of the anatomical ROIs used in the current analyses with the exception of the medial temporal lobe structures. With more specific ROIs, undetected relationships between performance and structure could emerge in parietal and prefrontal areas. In future studies, functional MRI data from a PM task could be used to directly define areas of interest to maximize sensitivity when looking for relationships between structure and behavior.

Finally, the number of subjects in our sample is a limitation. As such it may be that the relationship between the MTL and focal performance is simply the strongest or most consistent effect in the data. Increasing the sample size would boost the power to detect smaller effects that could have gone undetected in the current experiment. Moreover, examining neuropsychological performance in a larger sample would be useful in assessing potential mediating factors that may be influencing the present results, such as the influence of attention and other cognitive processes. A larger sample would also allow for the analysis of potentially interesting interactions of observed relationships with age and disease status. Despite these limitations, the present work indicates the value of examining the association between structural and behavioral measures and how this systematic examination in PM can address important and timely theoretical questions.

To the authors' knowledge, the work presented here is the first examination into the associations between regional volume and PM outside of neurological populations. As predicted by previous work (McDaniel & Einstein, 2011), the strongest behavior–structure relationship was between MTL volume, in particular the hippocampus, and focal PM accuracy. This relationship suggests an important role for the hippocampus in focal PM tasks. The novel results described here illustrate the beneficial aspects of examining anatomical and behavioral information in parallel and provide support for the neuropsychological implications of the multiprocess theory of PM (McDaniel & Einstein, 2011).

Acknowledgements

We thank the Clinical Core of the Washington University Knight Alzheimer's Disease Research Center for participant assessments and the Imaging Core for structural MRI data. This work was supported by the National Institutes of Health (P50 AG05861, P01 AG03991 and P01 AG026276). Brian A. Gordon, Jill T. Shelton, and Julie M. Bugg were supported by the National Institute of Aging (5T32AG00030).

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