Mental Paper Folding Performance Following Penetrating Traumatic Brain Injury in Combat Veterans: A Lesion Mapping Study

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Mental paper folding is a complex measure of visuospatial ability involving a coordinated sequence of mental transformations and is often considered a measure of mental ability. The literature is inconclusive regarding the precise neural architecture that underlies performance. We combined the administration of the Armed Forces Qualification Test boxes subtest measuring mental paper folding ability, with a voxel-based lesion symptom mapping approach to identify brain regions associated with impaired mental paper folding ability. Using a large sample of subjects with penetrating traumatic brain injury and defined lesions studied over 2 time points, roughly 15 and 35 years post-injury, enabled us to answer the causal questions regarding mental paper folding impairment. Our results revealed that brain injury significantly exacerbates the decline of performance on mental paper folding tasks over time. Our study adds novel neuropsychological and neuroimaging support for parietal lobe involvement; specifically the right inferior parietal lobule (Broadmann’s Area [BA] 40) and the left parahippocampal region (BAs 19, 36). Both areas were consistently associated with mental paper folding performance and demonstrate that the right parietal lobe and the left parahippocampal gyrus play an integral role in mental paper folding tasks.

Keywords: inferior parietal, left hippocampal gyrus, lesion analysis, mental paper folding, penetrating head injury

Introduction

Mental paper folding is a complex visual transformation task. Mental transformation of visual stimuli is a component of spatial ability, which has been considered a form of general intelligence or a “global measure of mental ability” (Uhlner and Bolanovich 1952, p. 11; Lohman 2000). Mental paper folding involves mentally imagining the folding of a 2-dimensional pattern into a mental representation of a 3-dimensional box, or mentally unfolding the 3-dimensional box into a 2-dimensional pattern. To complete a mental paper folding task, each fold requires a simple mental rotation of a square, from 2-dimensionality to 3-dimensionality creating a sequence of coordinated manipulation of the mental rotation and transformation components (Milivojevic et al. 2003). Both visual representation of the pattern and transformation in 3-dimensional space is essential to correctly answer a mental paper folding question. Mental rotation is a widely studied visuospatial measure; however, there is a continued lack of consensus regarding the precise neural structures that correlate with performance. Both mental rotation and mental paper folding are the subtypes of objective imagery control or spatial transformations, the ability to manipulate mental representations (Ekstrom et al. 1976; Lequerica et al. 2010). Mental rotation involves encoding internal spatial relations and correctly mentally transforming a visual stimulus.

Shepard and Metzler (1971) developed one of the first and most replicated pure mental rotation tasks, which involved rotating and matching 3-dimensional images of connected blocks. A year later, Shepard and Feng (1972) investigated a mental paper folding task, where subjects had to mentally refold a 2-dimensional pattern into a 3-dimensional box. Mental paper folding tasks were administered earlier than the 1970’s; however, they were not published in the scientific literature. For example, spatial relations tasks, including mental paper folding (i.e. both folding and unfolding patterns), were included in the army qualification tests as early as the 1950s to determine spatial abilities, a measure of general mental ability (Uhlner and Bolanovich 1952).

As the literature for mental paper folding is so limited, especially for brain injury populations, it is beneficial to discuss the neuroimaging and neuropsychological studies involving mental rotation, a repeated subcomponent of the mental paper folding task. Mental rotation tasks alone are also a compilation of different processes including visual encoding, rotating the object, comparing objects to assess whether they are the same, and responding (Cooper and Shepard 1973). Mental paper folding involves all of these components in addition to the actual mental folding, an added complexity. Wright et al. (2008) investigated the relationship between spatial tasks by using computerized adaptations of Shepard and Metzler’s (1971) mental rotation task and Shepard and Feng’s (1972) mental paper folding task. They found that the practice effects gained on a particular task, such as repeating the mental rotation task, would also lead to gains on the unpracticed mental paper folding task. The reverse was also true. Wright et al. (2008) demonstrated the important relation between both tasks, as there was a symmetrical practice transfer.

Identifying the brain structures required for the mental rotation and mental paper folding would require lesion studies to be able to assess causality and not simply correlation. In one of the first and few published studies on mental rotation involving brain-injured subjects, Ratcliff (1979) demonstrated that lesions to the right parietal cortex selectively impaired mental rotation. Three decades of research later, the accumulated evidence is still inconclusive, although more

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thorough, regarding the precise neural correlates of mental rotation and paper folding. Advances in neuroimaging have supported a greater understanding of the specific neural correlates activated by mental rotation and to a lesser extent mental paper folding. Theoretically, the intraparietal sulcus is assumed to be involved in mental rotation as it processes spatial information about the position and orientation (Andersen et al. 1997). In particular, the right inferior parietal lobules (Broadmann’s Area [BA] 40) have the most robust findings in recent neuroimaging studies for the mental rotation (Cohen et al. 1996; Harris et al. 2000; Milivojevic et al. 2003; Parsons 2003; Podzelenko et al. 2005; Gogos et al. 2010), which is substantiated by a recent meta-analysis (Zacks 2008). This is further supported by a diffusion tensor imaging study, which found a specific correlation between mental rotation performance and white matter organization in the anterior part of the intraparietal sulcus; high mental rotation performance was paralleled by high fractional anisotropy values in the posterior parietal region (Wolbers et al. 2006).

In terms of lateralization, while most of the literature supports a right hemispheric dominance, other neuroimaging studies argue that there is bilateral parietal activation (Carpenter et al. 1999; Booth et al. 2000; Podzelenko et al. 2002) or a left hemispheric dominance (Alivisatos and Petrides 1997) for mental rotation tasks. However, even for the studies that support bilateral parietal activation, there is often a finding of stronger activation in the right parietal lobe than the left (Carpenter et al. 1999; Podzelenko et al. 2002). Using event-related potentials (ERPs), Milivojevic et al. (2003) found that even though there was a right hemispheric activation for pure mental rotation, the left hemisphere was also involved when a complex sequence of transformations was required for mental paper folding. However, caution must be employed in interpreting the neural location of brain generators from scalp ERPs in isolation. In a later functional magnetic resonance imaging (fMRI) study, a more accurate methodology for determining precise brain localization of function, Milivojevic et al. (2009) found no hemispheric dominance for mental rotation. Based on the differential methodologies, it is more appropriate to interpret the fMRI results which demonstrate bilateral activity and no hemispheric dominance for the complex mental rotation rather than the highly lateralized findings of the previous ERP paper.

Other studies suggest that mental rotation tasks involve more than just rotation and propose figure segmentation as a component of rotation which implicates the inferior parietal lobules which border the parahippocampal areas associated with visual object part identification (e.g., Carpenter et al. 1999; Just et al. 2001; Schendan and Stern 2007). The parahippocampal region (BA 19) was also found to be consistently activated through the mental rotation of blocks, rather than hands (Kosslyn et al. 1998). Mental rotation of hands is an example of task-dependent neural correlates for mental rotation. Furthermore, Amick et al. (2006) suggest that there is a different strategy for viewer-centered transformation, which requires integrating motor imagery versus object rotation. Additionally, right basal ganglia lesions have also been associated with an impaired mental rotation (Harris et al. 2002) as well as motor cortex activation, although this was to a lesser degree supported by the meta-analysis (Zacks 2008).

Neuropsychological tasks have supported the neuroimaging findings and have consistently implicated the inferior parietal sulcus for mental rotation tasks (Ditunno and Mann 1990; Buiatti et al. 2011). A transcranial magnetic stimulation (TMS) study further demonstrates the importance of the right inferior parietal sulcus in mental rotation performance (Harris and Miniuassi 2003). The study found that the parietal cortex is involved in the spatial transformation, and not simply the perceptual processing of the image (Harris and Miniuassi 2003; Wolbers et al. 2006). Therefore, both neuroimaging and neuropsychological findings indicate that the mental rotation of objects, and thus mental paper folding, is dependent on the right intraparietal sulcus.

A variety of different patient populations suffering from neurological diseases or brain injury also demonstrate mental rotation impairment and can further facilitate the elucidation of neural correlates. Lee et al. (1998) found that Parkinson’s patients made significantly more errors than controls for 3-dimensional wire frame object rotation whereas there was no group difference for 2-dimensional object rotation, suggesting dissociation. More recent studies have shown that there was no difference in performance between Parkinson’s patients and controls for object rotation; however, Parkinson’s patients with greater left hemispheric dysfunction made more errors than controls for mental rotation of hands indicating that there might be distinct lateralized neural correlate differences between the tasks (Amick et al. 2006). Human immunodeficiency virus patients had clear impairments on both hand and object mental rotations compared with controls; however, their performance was better on mental hand rotation compared with object rotation (Oleson et al. 2007). The results of varied performance on mental hand versus mental object rotation performance suggest that certain neural structures may be implicated in specific rotation tasks, for example, the basal ganglia implicated in Parkinson’s may have a greater involvement in mental hand rotation compared with the involvement in object rotation (Amick et al. 2006). This also may suggest that brain-injured subjects with basal ganglia neurological insults may show the same pattern of impairment as Parkinson’s patients. Therefore, there appears to be somewhat task-dependent patterns of impairment, separating mental rotation of hands versus mental rotation of objects and 2-dimensional rotation from 3-dimensional rotation (Lee et al. 1998; Amick et al. 2006). Further study would be necessary to determine all of the specific patterns of rotation deficits that correlate with precise neurological areas.

Despite continued efforts to understand the neural correlates of mental rotation and mental paper folding, a consensus has not yet been reached as to which brain areas are definitively involved. The goal of this study was to determine the precise causal role of human brain structures in mental paper folding, a complex mental transformation that includes a series of pure mental rotation tasks in the 3-dimensional space. The results would have implications for a wider range of mental transformation tasks as performance has been shown to be transferable (Wright et al. 2008). Using novel behavioral and structural neuroimaging data from a unique, large population of male penetrating brain-injured subjects with defined brain lesions and neuropsychological data from matched controls assessed twice on the same task approximately 15 and 35 years post-brain injury, we were able to suggest a causal neural relationship implicated in this.
cognitive ability. We conducted a voxel-based lesion symptom mapping (VLSM) whole-brain analysis to identify which lesion areas corresponded with impaired mental paper folding ability, testing both the control and brain-injured groups twice. We report that over time, the brain-injury group exhibited a significantly exacerbated decline on mental paper folding tasks. In addition, our structural neuroimaging findings, consistent over 2 time points, support the involvement of the “right” inferior parietal lobe (BA 40) and the “left” parahippocampal gyrus (BA 19, 36) in the performance of mental paper folding tasks. There have been few previous studies using mental paper folding tasks even though the implications of determining the task’s precise neural correlates can help identify the brain regions that mediate other visually based mental transformation tasks (Milivojevic et al. 2003; Wright et al. 2008). This longitudinal study consisting of a large patient population with defined brain lesions enables the analysis of causal questions regarding the lifetime trajectory of brain injury consequences not possible with neuroimaging or cross-sectional studies alone.

Materials and Methods

Subjects

Subjects were taken from the Vietnam Head Injury Study (VHIS) registry, which is a long-term follow-up neuropsychological study comprised of American male veterans who suffered traumatic brain injuries (TBI) in the Vietnam War (n = 199) and control subjects that experienced combat in Vietnam but did not suffer brain damage (n = 55) (Raymont et al. 2011). The VHIS currently consists of 4 phases: Phase I occurred between 1967 and 1970 and served as an enrollment period. Phase II occurred between 1981 and 1984 at the Walter Reed Army Medical Center with 520 brain-injured veterans and 85 control veterans without head injury. Phase III occurred approximately 20 years later between 2003 and 2006 at the National Naval Medical Center in Bethesda, MD, United States of America, with 199 brain-injured and 55 normal control veterans participating, and Phase IV is currently underway. For this study, we compared the same group of brain-injured and control subjects at both Phase II and Phase III. For the purpose of clarity, we will refer to Phase II as “Chronic Time Point 1” and Phase III as “Chronic Time Point 2” as data were collected approximately 15 and 35 years, respectively, post-injury.

To exclude the possibility that impaired performance on mental paper folding tasks could be attributed to decreased performance ability in general, we precluded any subject who had significant impairment using a Wechsler Adult Intelligence Scale-third edition (WAIS-III; Wechsler 1997a) performance intelligence quotient (IQ) cutoff of 70 which indicates “extremely low” performance when it was administered at Chronic Time Point 2 (Silverman et al. 2010). Additionally, we excluded any individuals in the control and brain-injured groups who did not complete the first 3 phases of the task (pre-injury, Chronic Time Points 1 and 2). After these exclusions, the brain-injured (n = 156) and control groups (n = 29) were both assessed at 2 time points. The groups were matched according to age, level of education, handedness, working memory performance, object naming ability, and pre- and post-injury general intelligence (Table 1). Pre-injury general intelligence percentile scores were obtained from the Armed Forces Qualification Test (AFQT-7), which was administered to individuals upon entry into the military (Bayoff and Anderson 1963). The AFQT-7 was an updated version of the previous army screening tests and was designed and tested to provide a measure of general military trainability in addition to the measures of specific aptitudes and general intelligence (Uhlaner and Bolanovich 1952). Following the research design for previous forms, experimental test items in 4 content areas developed by the separate services were administered to 3000 Armed Forces personnel for item analysis and selection to develop a psychometrically sound measure based on both reliability and validity data. The final drafts of the test forms were administered to a representative sample of the mobilization population to use for standardization purposes and as a basis for conversion of test scores to percentile norms. The AFQT-7 correlated highly with preceding operational forms (r = 0.89) and was deemed a satisfactory alternate form for screening (Bayoff and Anderson 1963). Based on further experimentation with administration, instructions for the AFQT-7 were made shorter and simpler than for previous forms, with no loss in test effectiveness (Graffman et al. 1988). The AFQT-7 has been standardized extensively by the US Military and is highly correlated with the WAIS-III intelligence scores (Graffman et al. 1988). The International Review Board at the National Naval Medical Center and the National Institute of Neurological Disorders and Stroke approved the ongoing VHIS studies. All subjects gave their informed written consent.

Neuropsychological Testing

Normal control and brain-injured groups underwent a week-long neuropsychological test battery at the National Naval Medical Center in Bethesda, MD, United States of America. The test battery investigated a variety of general areas of cognitive functioning including memory, perception, and intelligence. The AFQT-7 consists of 100 questions divided into 4 subtests (vocabulary knowledge, arithmetic word problems, object-function matching, and boxes mental imagery). To assess mental paper folding, we utilized the boxes subtest of the AFQT-7, which served as our experimental measure of interest.

Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Brain-injured (n = 156)</th>
<th>Normal controls (n = 29)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years: mean ± SD)**</td>
<td>57.9 ± 2.8</td>
<td>58.2 ± 1.6</td>
<td>t = -0.55, P = 0.560</td>
</tr>
<tr>
<td>Education (years: mean ± SD)</td>
<td>14.7 ± 2.4</td>
<td>14.5 ± 2.5</td>
<td>t = 0.48, P = 0.620</td>
</tr>
<tr>
<td>Handedness (R:A:L)</td>
<td>129 : 5 : 22</td>
<td>22 : 1 : 6</td>
<td>x² = 4.00, P = 0.046</td>
</tr>
<tr>
<td>Pre-injury IQ (percentile ± SD)</td>
<td>62.9 ± 24.6</td>
<td>65.5 ± 22.6</td>
<td>t = -0.53, P = 0.600</td>
</tr>
<tr>
<td>Post-injury IQ (percentile ± SD)</td>
<td>67.3 ± 21.6</td>
<td>67.0 ± 23.7</td>
<td>t = -0.17, P = 0.358</td>
</tr>
<tr>
<td>WMS SP (mean ± SD)</td>
<td>10.4 ± 2.9</td>
<td>10.8 ± 2.3</td>
<td>t = -1.16, P = 0.282</td>
</tr>
<tr>
<td>VOSP CA (mean ± SD)</td>
<td>54.3 ± 5.9</td>
<td>58.14 ± 3.7</td>
<td>t = -1.59, P = 0.103</td>
</tr>
<tr>
<td>WAIS BD (mean ± SD)</td>
<td>9.4 ± 1.1</td>
<td>9.8 ± 0.5</td>
<td>t = -2.03, P &lt; 0.002</td>
</tr>
<tr>
<td>WAIS BD (mean ± SD)</td>
<td>10.1 ± 2.8</td>
<td>10.8 ± 2.3</td>
<td></td>
</tr>
</tbody>
</table>

Note: Handedness: R, right-handed; A, ambidextrous; L, left-handed; Pre-injury IQ: AFQT-7 Armed Forces Qualification Test percentile; Post-injury IQ: Wechsler Adult Intelligence Scale-Third Edition (WAIS-III); VOSP: Wechsler-III Verbal IQ; PO: WAIS-III Performance IQ; WMS: Wechsler Memory subtest percentile of WMS-III; WMS SP: Spatial Span subtest standard score of WMS-III; Boston Naming: Boston Naming Test Object Naming total score; VOSP CA: Visual Object and Space Perception Cube Analysis total score; WAIS BD: Block Design subtest standard score of WAIS-III.

**Age: years at Chronic Time Point 2.
designed by the military to assess for spatial relations. The entire test is administered with a 50-min time limit. Instructions are initially read out loud as the test-taker reads along and the multiple choice questions are presented visually following the standard practice of army qualification tests from the past (Bayoff et al. 1956). For the boxes subtest, the stimulus item is on the far left and the subject must choose the correct figure from the 4 choices to the right. There are 2 versions of questions, one requiring unfolding a box and the other requiring folding pattern to create a 3-dimensional figure (Fig. 1). AFQT-7 total correct subtest scores were collected during Chronic Time Points 1 and 2 in addition to the total AFQT-7 score assessed pre-injury which determined the pre-injury IQ percentile.

We administered both general and specific cognitive measures at Chronic Time Point 2. Our general cognitive measure, the WAIS-III, was subdivided into 3 different quotient standard scores and percentiles: Performance Intelligent Quotient (IQ), Verbal IQ, and Full IQ. In addition, we administered the Boston Naming Test, which assesses object naming and compared the total scores to ensure comparable brain-injured and normal control groups (Kaplan et al. 1983). Specific cognitive measures focused on the assessment of spatial working memory ability were also administered, including the Working Memory Subtest score of the Wechsler Memory Scale-third edition (WMS-III; Wechsler 1997b); the Visual Object and Space Perception Battery Cube Analysis subtest (VOSP; Warrington and James 1991), which involves a subject naming the number of blocks shown in a visual built cube display; the WAIS-III Block Design subtest consisting of motor manipulation and construction of different colored blocks to match a visual pattern; and the WMS-III Spatial Span subtest which is a spatial working memory task analogous to the auditory digit span.

**Computed Tomography (CT) Acquisition and Analysis**

Axial CT scans without contrast were acquired at the Bethesda Naval Hospital on a GE Medical Systems Light Speed Plus CT scanner. Structural neuroimaging data were then reconstructed with an in-plane voxel size of 0.4 x 0.4 mm, an overlapping slice thickness of 2.5 mm, and a 1-mm slice interval. We determined a lesion location and volume from the CT images by using the Analysis of Brain Lesion software (Makale et al. 2002; Solomon et al. 2007) which is implemented in MEDs v.3.44 (Medical Numeric) with enhancements to include the automated anatomical labeling (AAL) atlas (Lancaster et al. 2000; Tzourio-Mazoyer et al. 2002). For further information regarding the software, refer to Solomon et al. (2007).

Lesion volume was calculated by manually tracing the lesions in all relevant slices of the CT image in native space, summing the traced areas, and multiplying by slice thickness. The lesion tracing was performed by one investigator (V.R.) and then reviewed by an observer who was blind to the results of the clinical evaluation and neuropsychological testing (J.G.), enabling a reliable consensus regarding the boundaries of each subject’s lesion. The CT image of each individual’s brain was normalized to a CT template brain image in the Montreal Neurological Institute (MNI) space. The spatial normalization was performed with the automated image registration (AIR) algorithm (Woods et al. 1993), using a 12-parameter affine fit. Note that both the subject’s brain and the MNI template’s brain are first skull-stripped in order to maximize the efficacy of the AIR registration from the native space to MNI space. In addition, voxels inside the traced lesion were not included in the spatial normalization procedure. Afterwards, the percentage of AAL structures that were intersected by the lesion was determined by analyzing the overlap of the spatially normalized lesion image with the AAL atlas (Tzourio-Mazoyer et al. 2002).

Prior to more complex behavioral analysis, we considered the distribution of lesions in our sample. Individual’s normalized lesion as delineated on CT scans was used for the computation of a group lesion overlap and restricted all analyses to a minimum overlap of 4 brain-injured subjects at a given voxel (Glascher 2009; Fig. 2). The colorized image represents the overlapping lesions at each voxel. Since the power of voxel analysis reflects the regional distribution of vulnerability to brain injury, maximum power is observed in the frontal areas which are most often affected by penetrating traumatic brain injury (pTBI). In our sample, we also determined that the regions of interests including the right inferior parietal area and the left parahippocampal gyrus had adequate lesion overlap coverage.

Secondly, we conducted a VLSM whole-brain analysis for the AFQT-7 boxes subtest scores at both Chronic Time Points 1 and 2 (Bates et al. 2003; Rorden et al. 2007). Brain regions were mapped for areas in which a significant lesion-impairment relationship (i.e. the association between lesion location and deficits in mental paper folding performance at each voxel) was found by applying parametric t-tests with a 5% false discovery rate (FDR) corrected for multiple comparisons. Gyri were obtained by applying the AAL atlas (Tzourio-Mazoyer et al. 2002). To examine the specific neural correlates of mental paper folding, we analyzed the Talairach coordinates using the Talairach client (version 2.4.2) to identify the specific structures, volumes, Broadmann Area labels and to determine ranges of the output of the VLSM (Talairach and Tournoux 1988; Lancaster et al. 2000).

**Statistical Analysis**

Behavioral data analysis was carried out with a level of significance of P < 0.05 (2-tailed) for all analyses except when otherwise discussed. Our experimental measure for mental paper folding was the boxes subtest score from the AFQT-7. Correct answers were scored as 1, incorrect answers were scored as 0 and unanswered questions were scored as incomplete. In this study, the total correct score for each subject is considered the subtest score.

The association between brain injury and mental paper folding was examined using a 2 x 2 analysis of variance (ANOVA) with Time (Chronic Time Points 1 and 2) as a within-subjects factor and Group (brain-injured and normal control) as between-subjects factor. In planned follow-up analyses, the AFQT-7 boxes subtest scores for the 2 time points in brain-injured and normal control groups were compared using within-subjects paired t-tests with an t-tailed P-value (P < 0.05) due to the expected decline in mental rotation (and thus mental paper folding) with normal aging across both populations (normal aging; Corkin et al. 1989; Dror and Kosslyn 1994; Band and Kok 2000; brain-injured; Geiser et al. 2008; Raymont et al. 2008). Furthermore, we compared demographical and neuropsychological control measures between the experimental brain-injured and control groups using between-subjects t-tests.

**Results**

**Behavioral Results**

Demographic and neuropsychological outcome measures were compared to ensure that there were no confounding

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**Figure 1.** AFQT-7 boxes subtest. Sample of the questions asked in the boxes subtest of the AFQT-7. Both of these questions were presented as samples before the test was administered. The first question involves the mental paper folding in the form of matching and folding the template and matching it to the correct choice of folded box, in this case, B. The second question assesses the same procedure in the reverse, testing the ability to mentally unfold and rotate the box to match a template, the correct answer being A.
factors contributing to the results. The brain-injured and normal control groups did not differ significantly on age, level of education, handedness, working memory performance, object naming ability, or pre- and post-injury general intelligence (Table 1).

To evaluate the association between the brain-injured and normal control groups on the mental paper folding task, we compared the AFQT-7 boxes subtest scores at Chronic Time Points 1 and 2. The 2-way ANOVA repeated measures revealed a significant main effect for Group \( (F_{1,183} = 5.18, P < 0.024) \) and Time \( (F_{1,183} = 25.94, P < 0.001) \) as well as a significant interaction effect for Group × Time \( (F_{1,183} = 4.25, P < 0.041) \). Planned follow-up analyses revealed no significant difference between the 2 groups at Chronic Time Point 1 \( (F_{1,183} = 1.620, P = 0.145) \); however, brain-injured subjects performed significantly worse at Chronic Time Point 2 than the control group \( (F_{1,183} = 0.017, P < 0.005) \). Further, for the 2 chronic time points within each group, both brain-injured subjects and controls performed significantly worse at Chronic Time Point 2 compared with Chronic Time Point 1 (brain-injury group: \( t(155) = -8.79, P < 0.001, 1\)-tailed; control group: \( t(28) = 2.00, P < 0.028, 1\)-tailed) (Fig. 3).

The brain-injured group performed significantly worse on only one specific spatial working memory task; VOSP Cube Analysis \( (P < 0.002) \). The VOSP Cube Analysis total score correlated with the AFQT boxes subtest scores at both Chronic Time Point 1 \( (r = 0.30, P < 0.001) \) and Chronic Time Point 2 \( (r = 0.31, P < 0.001) \), indicating that lower values on the mental paper folding task correlated with lower VOSP Cube Analysis scores.

**Neuroimaging Results**

We conducted VLSM analyses based on the boxes subtest scores for Chronic Time Points 1 and 2. Figure 4 represents the specific anatomic locations where subjects performed poorly on the AFQT-7 boxes subtest; areas with a greater number of lesions correspond to brighter colorization. The peak lesion–deficit relationships at both time points are noted in Table 2. At Chronic Time Point 1, lesions that caused impairment in mental paper folding were found in the right inferior parietal lobule (BA 40) and the left parahippocampal gyrus (BA 19) (Fig. 4, Top). At Chronic Time Point 2, lesions that affected subtest scores in mental paper folding were more diffuse and included the right temporal lobe (BA 21), right insula (BA 13), right precentral gyrus (BA 4), in addition to the left parahippocampal gyrus (BA 36); and the right inferior parietal lobule (BA 40) as found during Chronic Time Point 1 (Fig. 4, Bottom).

**Discussion**

The present study investigated how mental paper folding is affected by brain injury over time. We used neuropsychological and neuroimaging data from a large sample of subjects
with pTBI with defined lesions, and neuropsychological data from combat-experienced controls over 2 chronic time points to assess and demarcate specific brain regions causally related to performance on mental paper folding tasks. Our results revealed that those with brain injuries had an exacerbated decline in performance compared with non-brain-injured controls on this mental paper folding task over time as expected (e.g., Raymont et al. 2008). Further, our study provides compelling evidence to support the involvement of the right inferior parietal lobule (BA 40) and left parahippocampal gyrus (BA 19 at Chronic Time Point 1, BA 36 at Chronic Time Point 2) as neural regions mediating mental paper folding performance.

The neuropsychological data demonstrated that both brain-injured and control groups showed a significant decrease in mental paper folding scores over time (comparing Chronic Time Points 1 and 2). The significant decline in mental paper folding performance for the control group is consistent with the previous reports of decreased performance levels for mental rotation, with increased age in normally aging populations (Dror and Kosslyn 1994; Band and Kok 2000; Geiser et al. 2008). This pattern of a significant performance decline with aging was also expected and found for the brain-injured patients supporting previous research (Ditunno and Mann 1990; Booth et al. 2000; Harris et al. 2002; Raymont et al. 2008).
Additionally, we found that overall, brain-injured subjects demonstrated an exacerbated decline on mental paper folding tasks compared with controls, as demonstrated by the significant interaction effect of Group and Time. These results echo an earlier study on the VHIS population (after the completion of Phase III), which suggested that an intensified decline in intelligence was a significant risk for those with a history of pTBI (Raymont et al. 2008). That report corroborated previous findings that suggested penetrating head injury in young adulthood exacerbates cognitive decline (Grafman et al. 1988; Corkin et al. 1989). Using a similar veteran population, Corkin et al. (1989) found that brain injury exacerbated cognitive decline in performance over time, irrespective of lesion site or cognitive test. Corkin et al. (1989) hypothesized that a reduction in cognitive abilities later in life results from the combination of the initial brain injury and secondary effects of the injury over time, as well as the effect of stress on the remaining brain tissue, suggesting that the brain functions are in a “compromised state” for decades after a TBI.

Using the VLSM whole-brain analysis, we were able to localize the neural regions of interest that were directly responsible for mental paper folding deficits at both time points, irrespective of any planned grouping methods. The 2 brain areas that showed a significant and consistent association to impairment on the mental rotation task were the right inferior parietal lobule (BA 40) and the left parahippocampal gyrus (BA 19, 36).

As there is well-documented support for the right parietal modulation of mental rotation tasks and thus assumed transfer to mental paper folding tasks, we will begin by discussing the left hemispheric findings. BAs 19 and 36 are centered around the parahippocampal area which has been previously associated with mental rotation performance (Zacks 2008). In 2 different PET studies measuring changes in regional cerebral blood flow with mental rotation task demands, there was increased activation found in the left parahippocampal gyrus (BA 19) as well (Kosslyn et al. 1998; Harris et al. 2000). Levin et al. (2005) found higher blood oxygenation level dependent activation for males in the left parahippocampal gyrus in addition to neural structures on the right (medial frontal gyrus, inferior parietal lobe, and inferior frontal gyrus) on a computerized mental rotation task. The study also found that the left parahippocampal gyrus was correlated with increased performance on the mental rotation task. There is still discussion as to whether BA 19 is implicated specifically in rotation, or rather is used in perception or object recognition, perhaps to geometrically parse the object or to enumerate the parts which is a necessary component for both mental rotation and mental paper folding (Schendan and Stern 2007). An fMRI study comparing mental rotation and object recognition found increased areas of activation in the parietal lobes for mental rotation and increased activity in the left BA 19 area for object recognition (Gauthier et al. 2002). Additionally, the left parahippocampal cortex is known for being used in spatial navigation. The parahippocampal place area is known for supporting perception of immediate scenes and so could theoretically play a role in mental rotation, as similar visual processes are used (Epstein et al. 2007). The research of Schendan and Stern (2007) also supports the involvement of bilateral parahippocampal place area activation during object mental rotation. The authors argue that the mental rotation task involves activation of the collateral-lingual sulci, which approximate the parahippocampal place area and may play a role in canonical recognition (Schendan and Stern 2008).

Although there is a transfer of practice effects between mental rotation and mental paper folding (Wright et al. 2008) and they are very similar tasks, there may be slight differences in terms of lateralization. Milivojevic et al. (2003) conducted a study using ERPs and found that during mental rotation tasks, the right parietal cortex was activated; however, mental paper folding tasks activated bilateral parietal regions indicated by scalp topographies. The authors suggest that greater involvement of the left hemisphere is needed for more complex transformations such as mental paper folding compared with pure mental rotation, which in a past ERP study was found to be lateralized to the right. However, stronger evidence in a later fMRI study, Milivojevic et al. (2009) found no hemisphere dominance for mental rotation tasks. Based on the stronger localization ability of an fMRI paradigm compared with an ERP paradigm, it would be more appropriate to assume that mental rotation tasks do not demonstrate lateralized dominance. Our results do not definitely answer the question of how the left parahippocampal gyrus (BA 19, 36) is involved in mental rotation, but do give evidence that lesions in that area correspond to worse performance and provide additional evidence for the functionality proposed by Schendan and Stern (2008). In addition to its role in canonical recognition, the lingual sulci might also mediate automatic processing efforts to map the final configuration of the stimuli to stored objects that possess some similarity to the task stimuli. Such mapping would potentially ease any subsequent retrieval of the stimuli for task or other undefined purposes.

The repeated, more robust and supported finding of the study is that the right inferior parietal lobule (BA 40) modulates mental rotation ability and thus is inevitably implicated in mental paper folding performance. The inferior parietal lobule has been shown to have a significant neuronal activation through fMRI and ERP, more intensely in the right hemisphere for mental rotation tasks (Cohen et al. 1996; Harris et al. 2000; Milivojevic et al. 2003; Parsons 2003; Podzebenko et al. 2005; Hugdahl et al. 2006; Gogos et al. 2010). Beyond neuroimaging, this area has been implicated in mental rotation, a repeated component of mental paper folding, by neuropsychological studies (Ditunno and Mann 1990; Amick et al. 2006; Buia et al. 2011) as well as TMS studies (Harris and Miniussi 2003).

Other studies have found different areas of activation implicated in mental rotation, in addition to the right parietal

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<td>Parietal</td>
<td>Inferior parietal lobule (40)</td>
<td>R 44 –52 52 1 746</td>
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<td>Temporal</td>
<td>Sub-gyral (21)</td>
<td>R 48 –12 –12 3 145</td>
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<td>Parietal</td>
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<td>Limbic</td>
<td>Parahippocampal gyrus (38) Insula (13)</td>
<td>L 38 –30 10 1 492 R 36 –14 22 1 54</td>
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Table 2: Talairach coordinates and labels of the peak lesion–deficit relationships for the boxes subtest total correct scores

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lobule, which have included contralateral hemispheric activation in the left inferior parietal cortex (Alivisatos and Petrides 1997), inferior temporal lobe activation (Carpenter et al. 1999; Just et al. 2001), medial superior precentral cortex activation relating to motor simulation (Zacks 2008), and basal ganglia (Harris et al. 2002; Amick et al. 2006; Oleson et al. 2007). These varying areas of activation could be grounded on differences in tasks administered and possibly mediated by complexity of the sequence of mental rotation tasks required to perform a mental folding task (Amick et al. 2006). Zacks (2008) reported that activity in the medial superior precentral cortex occurred particularly under conditions that favor motor simulation to perform the mental rotation tasks studied. Furthermore, there have been fMRI neuroimaging studies implicating a larger network of dorsal stream activation in mental rotation tasks (Carpenter et al. 1999; Just et al. 2001; Podzhezenko et al. 2002). A more recent fMRI study reported that object categorization and mental rotation share a common network of prefrontal, dorsal, and ventral regions of the posterior cortex which are also implicated in mental paper folding (Schendan and Stern 2007). This is also strongly supported by the lack of hemispheric dominance found in an fMRI study by Milivojevic et al. (2009) for mental rotation. Involvement of a larger network or framework may provide functional evidence regarding the combination of both the left parahippocampal gyrus and the right inferior parietal lobule modulating mental rotation through the different cognitive demands including object recognition, perception, and rotation required to accurately complete the task.

In terms of lesion area and volume, at Chronic Time Point 1, lesions that caused impairment in mental paper folding were found in the focal areas of the right inferior parietal lobule (BA 40) and the left parahippocampal gyrus (BA 19). At Chronic Time Point 2, we observe an increase in lesion areas and volume affecting subtest scores in mental rotation, which include the addition of BA 21, 13, and 4 while including the areas found at Chronic Time Point 1. This confirms previous studies that have shown that early brain injury may exacerbate cognitive decline (Corkin et al. 1989; Raymont et al. 2008). The exacerbated decline may be attributed to the effects of the chronic lesion plus the neuronal loss that accompanies normal aging (Raymont et al. 2008; Sidaros et al. 2009). In both the brain-injured and control groups, we expected some widespread neuronal and synaptic atrophy with aging (Salat et al. 2004). It is possible that the remaining brain area within the regions supporting mental paper folding recruited neurons from neighboring or contralateral cortex to perform the task. With aging and neuronal loss in those regions that provided neurons that helped our patients compensate for the effects of the original lesion, the effects of the lesion became more apparent and led to exacerbated decline. By measuring 2 very chronic time points 15 and 35 years post-injury, we have controlled for the effective restructuring and increased neuroplasticity that occurs within days or weeks of injury (Kleim and Jones 2008) which would enable some recovery of function to occur in the immediate post-injury period.

Mental paper folding is a complex task involving different visuospatial components including perception, possible object discrimination, and rotation. We assessed both brain-injured and normal control groups on a variety of specific spatial memory tasks; however, only the VOSP Cube Analysis showed a significant difference between the 2 groups. This might have occurred since it is the most similar task to the APQT-7 boxes subtest; involving a response as to how many cubes are presented in a visual stimulus. It requires the same perception of a similar 2-dimensional object and the ability to mentally rotate it in 3-dimensional space to acknowledging the number of different components. The other spatial working memory tasks were not significantly different between the groups, which support the theory that there may be specific regional brain involvement for task specific visuospatial manipulation needs. For example, Buiatti et al. (2011) did not use a mental rotation task requiring a matching strategy for response, which may have induced different cognitive processes compared with the ones required in our mental paper folding task. This could account for their findings of left prefrontal and right parietal lobe lesion patients showing impairment, whereas we found only right parietal or left parahippocampal lesions associated with consistent impairment in the mental paper folding task.

We were also limited by our mental paper folding task. While it did require the basic components of mental rotation and mental paper folding, the response of matching unfolded and folded cubes, does not cover the extent of all mental rotation or paper folding tasks. This is especially pertinent since studies have documented varied performance impairments depending on the cognitive operations required for specific mental rotation task (Lee et al. 1998). Additionally, there is minimal research available that focuses on mental paper folding and thus, our hypotheses were partially dependent on the mental rotation literature, which is a much simpler task. The research that has focused on mental paper folding has used both pen and paper tasks and computerized versions, which could introduce variation as well. Our study was completed with entirely male veterans in both brain-injured and normal control groups so we also cannot generalize our findings across genders. The literature indicates a robust difference in specific neural correlates between men and women on mental rotation tasks; (Thomsen et al. 2000; Roberts and Bell 2003; Geiser et al. 2008; Koscik et al. 2009). Even though fewer studies have shown a gender difference in performance and neural regions of activation for mental paper folding tasks, we would expect the same pattern due to the high correlation of performance between tasks (Levin et al. 2005; Wright et al. 2008). Additionally, there are limitations in the interpretation of lesion studies regarding the understanding of connectivity of white matter tracks, variance in lesion size, group averaging, and spatial resolution. Despite these limitations, our study provides an unique convergent evidence for the identification of key brain regions responsible for mediating visual mental transformations.

In conclusion, this study reliably demonstrates that lesions to the right inferior parietal and left parahippocampal brain regions cause a performance deficit on a mental paper folding task. We also found an exacerbated decline on this cognitive task for individuals with brain injury.

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Notes
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