Orbitofrontal Contributions to Human Working Memory

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Introduction

Accumulating functional neuroimaging evidence implicates the orbitofrontal cortex in working memory, demonstrating activity in this region for the coordination of multiple working memory operations (for meta-analytic reviews, see Wager and Smith 2003; Wager et al. 2004; Owen et al. 2005). The orbitofrontal cortex appears to mediate higher order processing requirements for working memory, enabling the joint maintenance, manipulation, and/or monitoring of information in working memory.

Keywords: lesion data, orbitofrontal cortex, prefrontal cortex, working memory

Materials and Methods

Participant Data

We drew participants from the Phase 3 Vietnam Head Injury Study registry, which includes American veterans who suffered brain damage from penetrating head injuries in the Vietnam War (n = 199), as well as neurologically healthy Vietnam veterans (n = 54). To preclude the possibility that impaired performance on working memory and executive function tests could be secondary to deficits in the production and/or comprehension of language, we excluded any participant who had significant impairment (defined as performance at least 2 standard deviations below the mean of the neurologically healthy group) on a test of language production and language comprehension (i.e., the Boston Naming test). From the remaining brain-injured veterans, we selected those with lesions involving significant damage to the orbitofrontal cortex, which comprises the ventral surface of the frontal cortex (Kringelbach 2005) (Fig. 1; n = 24). We additionally assessed a comparison group of brain-injured veterans whose damage was confined to the prefrontal cortex but did not involve orbitofrontal cortex (non-orbitofrontal cortex lesion group; n = 40), as well as neurologically healthy veterans (no lesion group; n = 54). Demographic and background cognitive function data for the 3 groups are presented in Table 1. No significant group differences were observed with respect to basic demographic variables (age, sex, and years of education), pre- and post-injury measures, and 3) exclusive use of verbal/auditory or nonverbal/spatial working memory tests. Thus, there has been no comprehensive evaluation of working memory function in a relatively large group of patients with damage specifically involving orbitofrontal cortex and across a broad range of tasks and stimulus material. The absence of such data represents a substantial gap in the understanding of both orbitofrontal cortex function and the neural substrates of working memory. Here, we characterize working memory function in a group of patients with orbitofrontal cortex lesions.

Lesion Analysis

We acquired computed tomography (CT) data during the Phase 3 testing period. Axial CT scans without contrast were acquired at the Bethesda Naval Hospital on a General Electric Medical Systems Light Speed Plus CT scanner in helical mode. We reconstructed the images with an in-plane voxel size of 0.4 × 0.4 mm, an overlapping slice thickness of 2.5 mm, and a 1-mm slice interval. We determined lesion location and volume from CT images using the Analysis of Brain Lesion Software (Makale et al. 2002; Solomon et al. 2007) contained in MEDx v3.44 (Medical Numerics) with enhancements to support the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al.
We defined the orbitofrontal cortex region of interest by applying anatomical landmarks and selecting patients with damage to the ventral surface of the frontal lobe. As part of this process, we spatially normalized the CT image of each subject’s brain to a template brain image in Montreal Neurological Institute space (Collins et al. 1994). We determined the percentage of AAL structures that the lesion entailed by analyzing the overlap of the spatially normalized lesion image with the AAL atlas image. We calculated lesion volume by manually tracing the lesion in all relevant slices of the CT image and then summing the traced areas and multiplying by slice thickness. The tracing technique isolated areas of missing brain and regions affected by metallic artifacts and penetrating objects. A trained neuropsychiatrist carried out the manual tracing, which was then reviewed by an observer that was blind to the results of the neuropsychological testing.

Neuropsychological Tests
We administered subtests of the Wechsler memory scale, third edition (WMS III; Wechsler 1997a), the Wechsler adult intelligence scale, third edition (WAIS III; Wechsler 1997b), and an experimental test of working memory, the n-back task (Cohen et al. 1993, 1997), to investigate the necessity of the orbitofrontal cortex for specific 1) cognitive operations (maintenance, manipulation, and monitoring) and 2) modalities of information (verbal and spatial) in working memory. Working memory “maintenance” refers to the temporary online retention of information and is measured by simple retention tasks (e.g., the digit span forward task). “Manipulating” items in working memory refers to the rearrangement and transformation of representations for goal-directed behavior and is measured by active retention tasks (e.g., the letter-number sequencing task). The joint maintenance, manipulation, and monitoring of items in working memory is investigated by executive control tasks that draw upon multiple components of working memory (e.g., the n-back task). The reported neuropsychological data from the WMS III and WAIS III represent standardized scores based on the published norms in Wechsler (1997a, 1997b). Data for the n-back task represent the mean number of errors in each patient group.

Maintenance Tasks
We investigated the patient’s ability to maintain information in working memory, administering a verbal/auditory maintenance measure, WMS III: spatial span forward task. In digit span forward, the patient hears a sequence of digits and attempts to repeat the sequence in order (Wechsler 1997b). In spatial span forward, the patient watches the examiner tap a sequence of locations on a board and attempts to repeat the tapping sequence in order (Wechsler 1997b). Together, these tasks provide an assessment of the simple retention of verbal/auditory and nonverbal/spatial representations in working memory.

Manipulation Tasks
We investigated the patient’s ability to manipulate items in working memory, employing 2 measures of the rearrangement of verbal/auditory information (WMS III: letter-number sequencing and WMS III: digit span backward) and a measure of the manipulation of nonverbal/spatial representations (WMS III: spatial span backward). In letter-number sequencing, the patient hears a sequence of alternating digits and letters and attempts to rearrange the order of each item by repeating the digits in numerical order followed by the letters in alphabetical order (Wechsler 1997a). Digit span backward (Wechsler 1997a) and spatial span backward (Wechsler 1997a) are the same as their forward counterparts, except that the subject attempts to repeat each sequence in reverse order. Together, these measures provide an assessment of the manipulation and rearrangement of verbal and spatial representations in working memory.

Joint Maintenance, Manipulation, and Monitoring Tasks
Accumulating neuroscience evidence implicates the orbitofrontal cortex in executive control processes underlying the coordination of multiple working memory operations (for meta-analytic reviews, see Wager and Smith 2003; Wager et al. 2004; Owen et al. 2005). We therefore investigated the patient’s ability to jointly maintain, manipulate, and monitor information in working memory, administering the n-back task. In this task, the patient receives a sequence of visually presented letters and indicates whether each letter matches the stimulus that appeared n trials previously (1-, 2-, or 3-back; Coelho et al. 1993, 1997). The n-back task provides a continuous recognition measure of the patient’s ability to 1) process and simultaneously monitor a series of stimuli, 2) maintain activation of recently processed and potentially relevant items, 3) discard recently processed but irrelevant information, and 4) make comparisons between various items in the series to identify a correct match. Thus, the n-back task examines the joint maintenance, manipulation, and monitoring of
information in working memory (for experimental validation of the n-back task in working memory, see Kane et al. 2007).

Reasoning Tasks
To investigate whether the orbitofrontal cortex is necessary for performance on reasoning tasks that do not exclusively depend on working memory, we administered neuropsychological tests of mental arithmetic (WAIS III: arithmetic) and visuospatial reasoning (WAIS III: matrix reasoning). In arithmetic (Wechsler 1997a), the subject hears numerical problems in story format, performs mental arithmetic (i.e., without paper and pencil), and provides a verbal response. In matrix reasoning, the patient receives pictures of geometric shapes and draws an analogical inference about the missing shape that completes the pattern (Wechsler 1997b). The inclusion of verbal and spatial reasoning tasks complements our analysis of these operations in working memory, supporting an assessment of the contribution of the orbitofrontal cortex to cognitive operations for manipulating information in a broader range of contexts.

Statistical Analyses
For each neuropsychological test, we conducted a one-way analysis of variance examining the performance of orbitofrontal lesion patients \((n = 24)\) relative to patients with prefrontal lesions not involving orbitofrontal cortex \((n = 40)\) and neurologically healthy participants \((n = 54)\). We then applied Tukey’s honestly significant difference test to determine significant between-group differences.

Results
To summarize the results reported in Table 2, no significant group differences in the orbitofrontal patient sample were observed for neuropsychological tests of working memory maintenance (digit span forward and spatial span forward) or manipulation (letter-number sequencing, digit span backward, and spatial span backward) or for measures of mathematical (arithmetic) or spatial reasoning (matrix reasoning). However, deficits were found in the orbitofrontal patient group for tests of working memory requiring the coordination of maintenance, manipulation, and monitoring processes (total errors for 1-back, 2-back, and 3-back). This pattern of findings suggests that the orbitofrontal cortex may be critical for executive control functions underlying the joint maintenance, manipulation, and monitoring of information in working memory. To substantiate this conclusion, however, it is necessary to further examine the anatomical specificity of the observed results.

Medial versus Lateral Orbitofrontal Cortex Lesions
As can be seen in Figure 1, the orbitofrontal patient group includes lesions involving medial and lateral aspects of the orbitofrontal cortex and, in approximately 5 or 6 cases, entails damage that extends beyond the orbitofrontal cortex. Thus, impaired performance in the orbitofrontal patient sample may reflect the contribution of medial and/or lateral prefrontal subregions or areas outside orbitofrontal cortex. To further isolate the specific orbitofrontal subregions underlying working memory function, we performed a supplementary analysis that specifically examined the relative importance of medial and lateral orbitofrontal subregions in working memory. We constructed 2 patient groups to examine this issue. First, we selected the subset of patients in the orbitofrontal sample whose lesions were highly focal, entailing selective damage to medial subregions that did not also encompass lateral orbitofrontal subregions \((n = 6; \text{Fig. 2})\). Second, we selected the subset of patients in the orbitofrontal sample with focal lesions primarily involving lateral orbitofrontal cortex (i.e., with minimal involvement of medial subregions; \(n = 12; \text{Fig. 3})\). Demographic and background cognitive function data for each patient group are presented in Table 3. No significant group differences were observed with respect to basic demographic variables (age, sex, and years of education), pre- and post-combat measures of cognitive function, post-combat measures of verbal IQ and verbal comprehension, and lesion size (Table 3). In summary, the focal patient groups were well matched with respect to 1) basic demographic variables, 2) pre- and post-combat measures of cognitive function, and 3) lesion size.

To determine the specific effect of medial versus lateral orbitofrontal damage on working memory, we compared the performance of the medial orbitofrontal patient group \((n = 6)\)
with the lateral orbitofrontal patient sample \( (n = 12) \) and neurologically healthy participants \( (n = 54) \). Because the assumptions underlying parametric statistics were not satisfied (Supplementary Table 1, Supplementary Figs 1–22), nonparametric statistics were applied to test for group effects and for pairwise comparisons. As Table 4 illustrates, no significant between-group differences were observed for tests of working memory maintenance (digit span forward and spatial span forward) or manipulation (letter–number sequencing, digit span backward, and spatial span backward) or for measures of mathematical (arithmetic) or spatial reasoning (matrix reasoning). However, neuropsychological tests involving the coordination of working memory maintenance, manipulation, and monitoring processes revealed significant deficits in the medial orbitofrontal patient group (total errors for 1-, 2-, and 3-back), relative to both the lateral orbitofrontal lesion sample and the neurologically healthy participant group, particularly at high levels of cognitive load (2-back and 3-back). Lateral orbitofrontal lesions were not associated with pervasive deficits on the administered working memory measures. This pattern of findings indicates that the medial orbitofrontal cortex is critical for executive control functions underlying the joint maintenance, manipulation, and monitoring of information in working memory.

**Discussion**

The aim of the current study was to investigate the necessity of the orbitofrontal cortex for key competencies of working memory. Using a relatively large sample of patients with orbitofrontal damage \( (n = 24) \) and a wide-ranging assessment of cognitive function, we report several main findings: 1) medial

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**Table 3**

Demographic and background data

<table>
<thead>
<tr>
<th>Group</th>
<th>Medial OFC ( (n = 6) )</th>
<th>Lateral OFC ( (n = 12) )</th>
<th>No lesion ( (n = 54) )</th>
<th>Kruskal-Wallis ( \chi^2 )</th>
<th>Kruskal-Wallis ( P ) value</th>
<th>Significant between-group differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57.83 (1.47)</td>
<td>59.25 (3.31)</td>
<td>59.52 (3.42)</td>
<td>2.62</td>
<td>0.27</td>
<td>None</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>n/a</td>
<td>n/a</td>
<td>None</td>
</tr>
<tr>
<td>Years of education</td>
<td>14.00 (3.16)</td>
<td>13.08 (2.99)</td>
<td>15.19 (2.47)</td>
<td>4.50</td>
<td>0.11</td>
<td>None</td>
</tr>
<tr>
<td>Pre-combat AFQT</td>
<td>56.50 (23.46)</td>
<td>53.91 (27.86)</td>
<td>65.40 (22.91)</td>
<td>2.06</td>
<td>0.36</td>
<td>None</td>
</tr>
<tr>
<td>Post-combat AFQT</td>
<td>57.50 (24.96)</td>
<td>74.78 (17.22)</td>
<td>72.34 (22.99)</td>
<td>2.45</td>
<td>0.29</td>
<td>None</td>
</tr>
<tr>
<td>Post-combat verbal IQ</td>
<td>104.17 (8.83)</td>
<td>104.42 (12.48)</td>
<td>109.87 (12.38)</td>
<td>2.64</td>
<td>0.27</td>
<td>None</td>
</tr>
<tr>
<td>Post-combat verbal comprehension</td>
<td>103.83 (10.87)</td>
<td>105.33 (13.92)</td>
<td>109.66 (12.04)</td>
<td>2.03</td>
<td>0.36</td>
<td>None</td>
</tr>
<tr>
<td>Total percent volume loss ( (cm^3) )</td>
<td>2.26 (0.73)</td>
<td>2.26 (1.10)</td>
<td>0.00 (0.00)</td>
<td>71.15</td>
<td>0.00</td>
<td>Medial OFC &gt; no lesion</td>
</tr>
</tbody>
</table>

Note: OFC, orbitofrontal cortex; n/a, not applicable. Data are presented as means with standard deviations in parentheses. "Age" refers to age at the time of Phase 3 evaluation. "Sex" refers to the percentage of male veterans. "Years of education" refers to the total number of years of education the veterans completed. "Pre-combat AFQT" refers to index scores on the Armed Forces Qualification test, a battery of tests measuring basic cognitive function at the time of enlistment (pre-injury). "Post-combat AFQT" refers to index scores on the AFQT administered at Walter Reed Medical Center after injury. "Post-combat verbal IQ" refers to the Phase 3 verbal IQ index score from the WAIS. "Post-combat verbal comprehension" refers to the Phase 3 verbal comprehension index score from the WAIS. Nonparametric statistics were used to test for group effects and for the pairwise comparisons given the small number of participants in each sample. Significant between-group differences were determined with the Mann–Whitney U test, \( P < 0.05 \).

**Table 4**

Neuropsychological tests of working memory and reasoning

<table>
<thead>
<tr>
<th>Group</th>
<th>Medial OFC ( (n = 6) )</th>
<th>Lateral OFC ( (n = 12) )</th>
<th>No lesion ( (n = 54) )</th>
<th>Kruskal-Wallis ( \chi^2 )</th>
<th>Kruskal-Wallis ( P ) value</th>
<th>Mann–Whitney U</th>
<th>Mann–Whitney U ( P ) value</th>
<th>Significant between-group differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit span forward</td>
<td>6.83 (1.17)</td>
<td>6.50 (0.91)</td>
<td>6.68 (1.22)</td>
<td>0.69</td>
<td>0.71</td>
<td>n/a</td>
<td>n/a</td>
<td>None</td>
</tr>
<tr>
<td>Spatial span forward</td>
<td>7.83 (2.99)</td>
<td>10.00 (1.97)</td>
<td>10.22 (2.70)</td>
<td>4.06</td>
<td>0.13</td>
<td>n/a</td>
<td>n/a</td>
<td>None</td>
</tr>
<tr>
<td>1-Back errors</td>
<td>3.67 (1.97)</td>
<td>3.25 (2.38)</td>
<td>2.57 (2.48)</td>
<td>2.72</td>
<td>0.26</td>
<td>n/a</td>
<td>n/a</td>
<td>None</td>
</tr>
<tr>
<td>2-Back errors</td>
<td>6.83 (1.94)</td>
<td>4.75 (2.92)</td>
<td>3.85 (2.39)</td>
<td>9.46</td>
<td>0.00</td>
<td>40.50</td>
<td>0.00</td>
<td>Medial OFC &gt; no lesion</td>
</tr>
<tr>
<td>3-Back errors</td>
<td>8.00 (2.28)</td>
<td>5.38 (1.30)</td>
<td>4.68 (2.40)</td>
<td>8.39</td>
<td>0.01</td>
<td>48.50</td>
<td>0.00</td>
<td>Medial OFC &gt; no lesion</td>
</tr>
<tr>
<td>Total errors for 1-, 2-, and 3-Back</td>
<td>6.17 (2.71)</td>
<td>4.46 (2.38)</td>
<td>3.70 (2.56)</td>
<td>13.94</td>
<td>0.00</td>
<td>7.50</td>
<td>0.03</td>
<td>Medial OFC &gt; no lesion</td>
</tr>
<tr>
<td>Letter-number sequencing</td>
<td>9.17 (1.84)</td>
<td>9.67 (2.31)</td>
<td>11.04 (2.68)</td>
<td>5.76</td>
<td>0.06</td>
<td>n/a</td>
<td>n/a</td>
<td>None</td>
</tr>
<tr>
<td>Digit span backward</td>
<td>5.00 (1.09)</td>
<td>4.58 (0.79)</td>
<td>4.96 (1.41)</td>
<td>0.73</td>
<td>0.69</td>
<td>n/a</td>
<td>n/a</td>
<td>None</td>
</tr>
<tr>
<td>Spatial span backward</td>
<td>10.33 (1.37)</td>
<td>11.60 (2.79)</td>
<td>12.02 (3.12)</td>
<td>1.34</td>
<td>0.51</td>
<td>n/a</td>
<td>n/a</td>
<td>None</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>10.33 (2.73)</td>
<td>10.50 (2.71)</td>
<td>11.00 (2.25)</td>
<td>0.62</td>
<td>0.73</td>
<td>n/a</td>
<td>n/a</td>
<td>None</td>
</tr>
<tr>
<td>Matrix reasoning</td>
<td>11.00 (2.97)</td>
<td>11.90 (3.14)</td>
<td>12.28 (2.94)</td>
<td>1.07</td>
<td>0.59</td>
<td>n/a</td>
<td>n/a</td>
<td>None</td>
</tr>
</tbody>
</table>

Note: OFC, orbitofrontal cortex; n/a, not applicable. Means are presented with standard deviations in parentheses. Because the assumptions of parametric statistics were not satisfied (Supplementary Table 1, Supplementary Figs 1–22), nonparametric statistics were used to test for group effects and for the pairwise comparisons. Significant between-group differences were determined with the Mann–Whitney U test, \( P < 0.05 \).
orbitofrontal lesions are associated with reliable deficits in executive control functions underlying the joint maintenance, manipulation, and monitoring of information in working memory, particularly at high levels of cognitive load; 2) medial orbitofrontal lesions are not associated with pervasive deficits for tests of working memory maintenance or manipulation; 3) medial orbitofrontal lesions are not associated with reliable deficits in tests of verbal or spatial reasoning; 4) lateral orbitofrontal lesions do not yield significant impairment in working memory function. Together, these results indicate that the neural architecture of the medial orbitofrontal cortex is computationally necessary for the coordination of working memory maintenance, manipulation, and monitoring processes.

Accumulating evidence indicates that the orbitofrontal cortex mediates executive control functions underlying the coordination of multiple working memory processes (for meta-analytic reviews, see Wager and Smith 2003; Wager et al. 2004; Owen et al. 2005). According to this framework, the orbitofrontal cortex is engaged when problems involve more than one discrete cognitive process, namely, when the application of one cognitive operation is not sufficient to solve the problem and the integration of 2 or more separate cognitive operations is required to fulfill the higher behavioral goal. The n-back task is an ideal example of such conditions, requiring the participant to simultaneously monitor a series of stimuli, maintain activation of recently processed and potentially relevant items, discard recently processed but irrelevant information, and make comparisons between various items in the series to identify a correct match. Multiple cognitive operations can be carried out successfully only if they are coordinated, and it is suggested that the coordination of information processing and information transfer between multiple operations is an important aspect of orbitofrontal cortex function.

Extensive functional neuroimaging data support this conclusion, demonstrating that the orbitofrontal cortex mediates higher order processing requirements for goal-directed behavior across several cognitive domains, including working memory (Wager and Smith 2003; Wager et al. 2004; Owen et al. 2005), planning and subgoal processing (e.g., Koecchlin et al. 1999), relational integration (Christoff et al. 2001; Kroger et al. 2002; Patterson & BarbeY, forthcoming), and social and emotional processing (e.g., Amodio and Frith 2006; BarbeY et al. 2009a, 2009b, forthcoming; Krueger et al. 2009; Passingham et al. 2009; BarbeY and GraYman forthcoming a, forthcoming b), and for the evaluation of reward-based contingencies in prediction and decision making (e.g., BechYra et al. 1999; Manes et al. 2002; Sanfet et al. 2003; Camille et al. 2004; Fellows and Farah 2005; Hsu et al. 2005). The observed functional profile of orbitofrontal cortex suggests that this region is critical for the coordination of multiple cognitive operations, particularly the monitoring and flexible updating of dynamic task-relevant information, thus providing a nexus for the integration of social, affective, and cognitive representations underlying executive control and goal-directed decision making. The shared role of orbitofrontal cortex in working memory and reward-related behavior further indicates that these processes are fundamentally linked, suggesting that working memory operations may have evolved from or co-opted neural mechanisms for the representation and processing of reward—increasing the likelihood that cognitive operations could be sustained over longer periods of time to support goal achievement and attainment of rewards.

Our neuropsychological patient data further complement the nonhuman primate (e.g., Jacobsen 1936; Malmo 1942; Butters and Pandya 1969; Butters et al. 1971, 1972; Goldman-Rakic 1987, 1995; Fuster 1997; Levy and Goldman-Rakic 1999, 2000) and functional neuroimaging literatures (e.g., Pett et al. 1995; D’Esposito and Postle 1999; Muller et al. 2002; Bald and Dronkers 2006; D’Esposito et al. 2006; Vollet et al. 2008; TsuYida and Fellows 2009), which have traditionally focused on dorsal and ventrolateral prefrontal contributions to working memory. The reported findings are consistent with the observed involvement of the dorsolateral prefrontal cortex in the manipulation of information in working memory (i.e., impairments in the letter–number sequencing task for the non-orbitofrontal lesion group are primarily attributable to dorsolateral prefrontal lesions involving Brodmann area 9; BarbeY AK, Colom R, Krueger F, GraYman J, unpublished data; BarbeY AK, Koenigs M, GraYman J, unpublished data). Our results, however, failed to corroborate neuroscience evidence implicating the ventrolateral prefrontal cortex in the maintenance of information in working memory, suggesting that this region may not be a necessary component of the neural systems mediating human working memory. Although this finding is consistent with functional neuroimaging evidence (i.e., the ventrolateral prefrontal cortex may be associated with but not necessary for working memory), divergence from the nonhuman primate literature may reflect significant macroscopic anatomical differences known to prevent mapping the precise localization of working memory function from monkeys to humans (e.g., Fuster 1997; Petrides 2000, 2005).

In conclusion, our findings elucidate a central component of the neural architecture of working memory, demonstrating that the medial orbitofrontal cortex is necessary for the coordination of working memory maintenance, manipulation, and monitoring processes. Although the computational bases of working memory operations remain to be fully characterized (i.e., uncovering algorithms for the active maintenance, manipulation, and monitoring of items in working memory), our findings provide key evidence for the neural architecture of these cognitive processes. The results of our neuropsychological patient study, together with emerging functional neuroimaging evidence, indicate that the medial orbitofrontal cortex is necessary for key competencies of working memory and demonstrate that this prefrontal subregion is a central component of the neural systems underlying the joint maintenance, manipulation, and monitoring of representations for goal-directed behavior.

Supplementary Material

Supplementary material can be found at http://www.cercor.oxfordjournals.org/. See also http://www.DecisionNeuroscienceLab.org/.

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Notes

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**References**


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