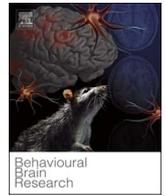




Contents lists available at ScienceDirect

## Behavioural Brain Research

journal homepage: [www.elsevier.com/locate/bbr](http://www.elsevier.com/locate/bbr)

## Research report

## Brain activity related to working memory for temporal order and object information

Brooke M. Roberts<sup>a</sup>, Laura A. Libby<sup>b</sup>, Marika C. Inhoff<sup>b,\*</sup>, Charan Ranganath<sup>a,b</sup><sup>a</sup> Center for Neuroscience, University of California at Davis, Davis, CA 95618, United States<sup>b</sup> Department of Psychology, University of California at Davis, Davis, CA 95616, United States

## ARTICLE INFO

## Keywords:

Temporal order  
Working memory  
Hippocampus  
Medial temporal lobe  
Prefrontal cortex  
fMRI

## ABSTRACT

Maintaining items in an appropriate sequence is important for many daily activities; however, remarkably little is known about the neural basis of human temporal working memory. Prior work suggests that the prefrontal cortex (PFC) and medial temporal lobe (MTL), including the hippocampus, play a role in representing information about temporal order. The involvement of these areas in successful temporal working memory, however, is less clear. Additionally, it is unknown whether regions in the PFC and MTL support temporal working memory across different timescales, or at coarse or fine levels of temporal detail. To address these questions, participants were scanned while completing 3 working memory task conditions (Group, Position and Item) that were matched in terms of difficulty and the number of items to be actively maintained. Group and Position trials probed temporal working memory processes, requiring the maintenance of hierarchically organized coarse and fine temporal information, respectively. To isolate activation related to temporal working memory, Group and Position trials were contrasted against Item trials, which required detailed working memory maintenance of visual objects. Results revealed that working memory encoding and maintenance of temporal information relative to visual information was associated with increased activation in dorsolateral PFC (DLPFC), and perirhinal cortex (PRC). In contrast, maintenance of visual details relative to temporal information was characterized by greater activation of parahippocampal cortex (PHC), medial and anterior PFC, and retrosplenial cortex. In the hippocampus, a dissociation along the longitudinal axis was observed such that the anterior hippocampus was more active for working memory encoding and maintenance of visual detail information relative to temporal information, whereas the posterior hippocampus displayed the opposite effect. Posterior parietal cortex was the only region to show sensitivity to temporal working memory across timescales, and was particularly involved in the encoding and maintenance of fine temporal information relative to maintenance of temporal information at more coarse timescales. Collectively, these results highlight the involvement of PFC and MTL in temporal working memory processes, and suggest a dissociation in the type of working memory information represented along the longitudinal axis of the hippocampus.

## 1. Introduction

Recent neuroscience research has revealed much about the neural mechanisms of working memory (WM), with several studies showing that the active maintenance of different types of sensory information is associated with a network of frontal and posterior brain regions. These results are in line with many frameworks that conceptualize WM maintenance processes as the activation of representations that are used to support perception and action [1–8]. More specifically, current models suggest that goal-directed executive control processes may be supported by frontal association areas, whereas representations of the perceptual features of maintained stimuli are concentrated in posterior

cortical regions (for review see [9,6,8]). In this way, WM serves as an interface between perception, cognition, and action, calling upon representations of different types of perceptual information in the service of future behavior.

Interestingly, whereas behavioral studies of WM have historically focused on the retention of temporal sequences of items such as digit sequences [10–13], the neuroscience literature has largely focused on WM for item features such as location, color, or shape [14]. As a result, relatively little is known about the neural mechanisms by which temporal information is encoded and maintained, particularly for non-verbalizable materials. Available evidence suggests that prefrontal areas could play a critical role in encoding and maintenance of

\* Corresponding author at: 1544 Newton Court, Davis, CA 95618, United States.

E-mail addresses: [brkroberts@ucdavis.edu](mailto:brkroberts@ucdavis.edu) (B.M. Roberts), [inhoff@ucdavis.edu](mailto:inhoff@ucdavis.edu) (M.C. Inhoff).<http://dx.doi.org/10.1016/j.bbr.2017.05.068>

Received 3 March 2017; Accepted 31 May 2017

0166-4328/© 2017 Elsevier B.V. All rights reserved.

temporal order information. Convergent evidence from lesion [15–17] and functional magnetic resonance imaging (fMRI) [18–21] have implicated PFC in long-term memory for temporal order, suggesting that it may also contribute to temporal WM. Consistent with this idea, single-unit recording studies of WM in nonhuman primates have demonstrated that populations of prefrontal neurons code for information about serial position in temporal sequences of objects [22] or locations [23]. More recently, human electroencephalography (EEG) studies have found increased oscillatory activity in the theta band (4–8 Hz) over frontal electrode sites during active maintenance of temporal order information [24,25], although it is not clear whether these oscillations originate from PFC.

A few fMRI studies have examined WM for temporal order [26], finding evidence for posterior parietal involvement. For instance Marsuetz and colleagues demonstrated that activation posterior parietal cortex is increased during a temporal order WM task relative to an item WM task [79]. Studies have also implicated posterior parietal cortex and provided evidence that the same network is recruited regardless of the type of stimuli that is to be maintained [27,28].

Despite these advances in understanding the neural basis of temporal WM, important questions remain. First, what is the broader circuitry involved in temporal WM? Some evidence suggests that, in addition to prefrontal and parietal areas, the hippocampus might play a role. For instance, findings from lesion studies in rats [29,30] and monkeys [78] have indicated that hippocampal lesions can impair long-term memory for temporal order, even when item memory is preserved. Converging evidence for hippocampal involvement in temporal order processes has also come from work in patients with hippocampal lesions. Specifically, individuals with hippocampal damage show greater deficits in order WM relative to item WM [31,32] and an impaired ability to make fine-grained temporal distance judgments [33]. Recent fMRI studies also suggest a role for the hippocampus in learning and retention of temporal sequences of visual objects and auditory stimuli in healthy adults [34–36]; (see [37] for a review).

Recent evidence suggests that the hippocampus exhibits different activation profiles and patterns of connectivity along the longitudinal axis [38,39], see [40] for a review), suggesting that there may be important functional differences between the anterior and posterior hippocampus. However, the extent to which the anterior and posterior extent of the hippocampus might differentially support the active encoding and/or maintenance of temporal and visual item information across short delays remains unclear.

Another open question is the extent to which some brain areas might support active maintenance of hierarchically organized temporal information across different timescales. Evidence for the hierarchical organization of temporal information comes from a number of behavioral investigations. Research on phonological WM indicates that timing information is used to group items in a sequence (e.g., in a U.S. telephone number, the first three digits are typically grouped separately from the last four digits), so that the temporal position of an item is linked to identity with a particular group of items (e.g., [41,42]). Interestingly, experiments that encourage the parsing of items into groups have found that memory for items within a particular group or memory for items at a specific position within the group can be remembered or forgotten independently [13]. For example, transpositions, a common error in serial recall, are characterized by interchanging items at the same relative position between different groups (see [12]). In this case, one may remember the time of day that an event occurred, but not the day of the week. In another situation, one may remember that an event occurred within a specific year, but not remember the precise month or day of the event. Evidence from neuroimaging also suggests that encoding information into groups is differentially processed compared to ungrouped information. Specifically, grouping of auditory stimuli relies more upon activation in parietal cortex [43]. There is a lack of neuroimaging data, however, regarding the neural mechanisms that support the maintenance of temporal order across varying, hierarchically

organized timescales.

In order to address these questions, we used event-related fMRI to investigate brain activity associated with encoding and maintenance of hierarchically organized temporal sequences of non-verbalizable objects. Participants were presented with two conditions designed to probe temporal WM processes: “Group” trials required the maintenance of coarse temporal information, while “Position” trials required the maintenance of detailed temporal information. To provide a link to extant fMRI studies of visual WM and to isolate processes associated with temporal WM, “Item” trials were also included. These trials required participants to maintain only visual details of non-verbalizable objects across a delay period. To identify brain regions selectively involved in WM for temporal order, brain activation related to maintenance of temporal order information (Group + Position trials) was contrasted against maintenance of detailed object information (Item trials). To identify regions that displayed sensitivity to the hierarchical organization of temporal associations, activation was compared between trials requiring maintenance of coarse (Group) and fine-grained (Position) information.

## 2. Materials and methods

### 2.1. Participants

20 Healthy undergraduate subjects were recruited from the University of California, Davis community, ranging in age from 18 to 30, with a mean age of 23. Ten participants were females. All were right handed. Data from two subjects were excluded due to poor memory performance (< 50% correct on any trial type), and data from one subject was excluded due to excessive motion. The remaining 17 subjects were included in the final analysis. The study was approved by the Institutional Review Board at the University of California, Davis. Written informed consent was obtained from each subject before the experiment.

### 2.2. WM task

The WM task (Fig. 1) was presented during fMRI scanning using Presentation (<http://nbs.neuro-bs.com/>) software. Stimuli consisted of unique kaleidoscope images (see [44]) presented on a black background. Kaleidoscope images were sorted into sets of four stimuli containing similar visual characteristics, including similar colors and shapes. Sets of kaleidoscope images were randomly assigned to one of three task conditions: two temporal conditions (coarse and fine temporal scales) and one item condition. Participants were familiarized with the task prior to the scan during a practice period. Experimental trials began with an instruction slide (1500 ms) indicating condition, followed by an encoding period containing two groups of two kaleidoscope images, all presented sequentially (1500 ms each), delineated by slides indicating whether images were part of Group 1 or Group 2 (1500 ms each). Within the encoding period, the interstimulus interval was 500 ms. In the Group condition (coarse temporal scale), participants were instructed to attend to and maintain which images were part of Group 1 and which were part of Group 2. In the Position condition (fine temporal scale), participants attended to and maintained the position of each image within a group (first or second). In the Item condition, participants attended to and maintained the visual features of the images, regardless of group. Following a delay period of 8 s, a probe consisting of a single kaleidoscope image was presented in the center of the screen for 2 s, and participants were instructed to make a response on a numbered response pad (test period). For Group trials, subjects indicated in which group the probe was presented. Subjects pressed “1” for group 1, and “2” for group 2. For Position trials, subjects indicated whether the probe was presented first or second within its group. Subjects pressed “1” if it was presented first, and “2” if it was presented second. For Item trials, subjects indicated if the probe was studied in

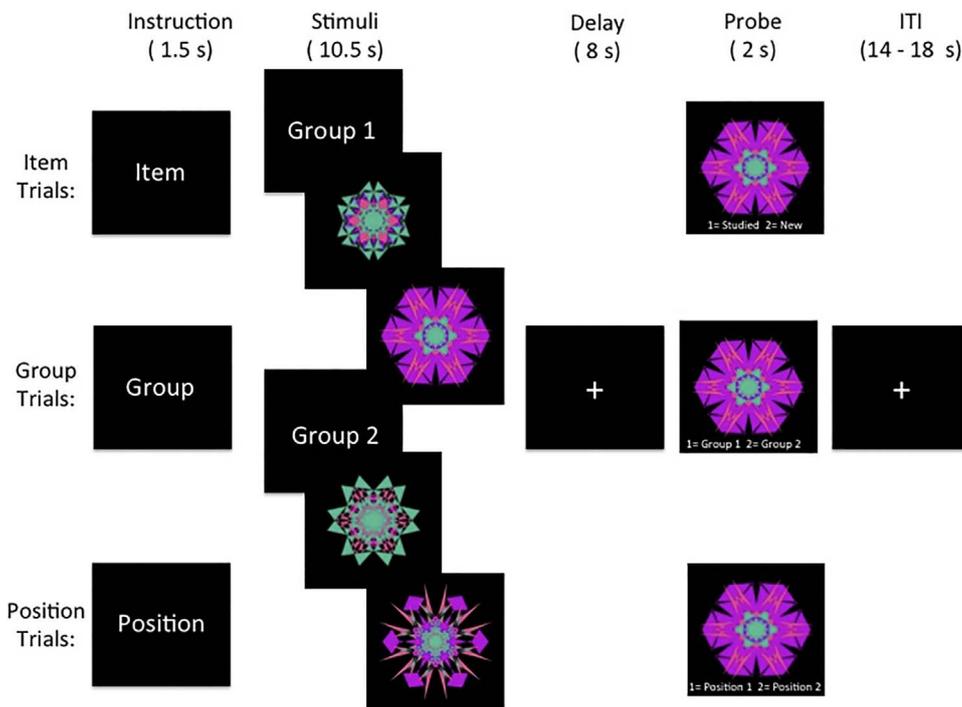


Fig. 1. Example stimuli and timing of Item, Group, and Position trials.

that trial. In half of the Item trials, the probe was presented in the trial, and in the other half of Item trials, the probe was a similar foil. Subjects pressed “1” if the item was studied, and “2” if it was not studied. Each trial ended with a variable inter-trial interval lasting 14–18 s.

The order of Group, Position, and Item trials was counterbalanced across participants. In total, there were 120 trials, with 40 trials each of Group, Position, and Item trials, broken down equally into eight testing blocks (15 trials per block). One participant was unable to complete the final block of testing due to time constraints, and so data from the first 7 blocks are included for that individual.

### 2.3. fMRI data acquisition

Images were acquired at the University of California, Davis Imaging Research Center on a 3T Siemens Tim Trio whole body MRI scanner equipped with a 32-channel phased array head coil. Pre-screening interviews ensured safety in the scanner, and all subjects were given earplugs to attenuate scanner noise. Padding and adjustable head restraints were used to minimize head motion. Imaging protocols included acquisition of a high-resolution T1-weighted whole-brain scan using a 3D magnetization-prepared rapid gradient-echo (MP-RAGE) sequence (matrix size =  $256 \times 256$ , voxel size =  $0.9 \times 0.9 \times 0.9$  mm<sup>3</sup>, number of slices = 208. Images sensitive to BOLD contrast were acquired with a gradient-echo echoplanar imaging (EPI) pulse sequence (TR = 2s, TE = 25 ms, FA = 90, FOV = 22 cm, matrix:  $64 \times 64$ , voxel size:  $3.4 \times 3.4 \times 3.4$  mm, number of slices: 36).

### 2.4. fMRI data analysis

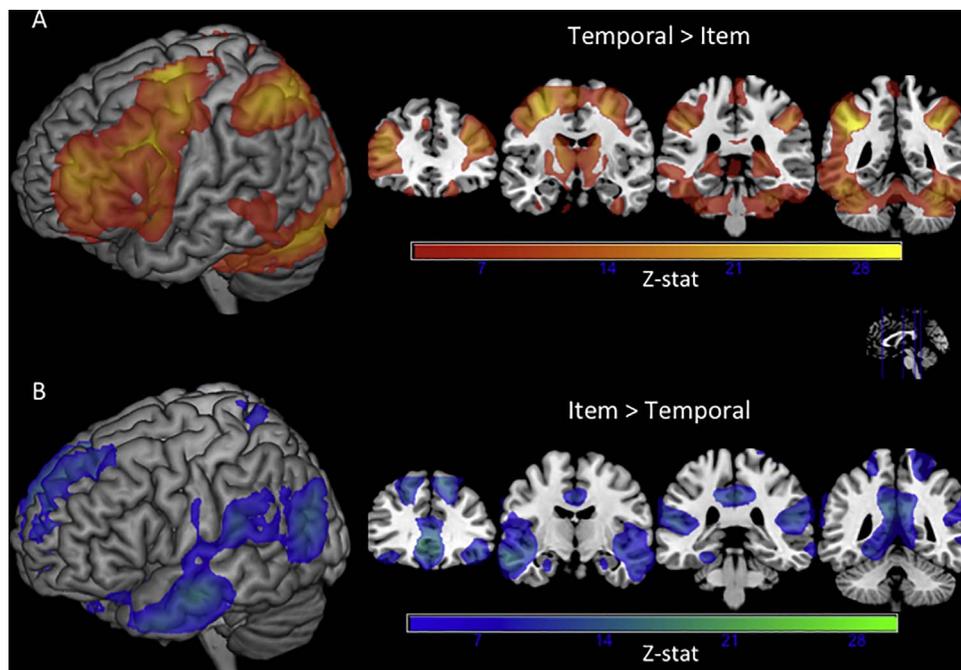
fMRI data analysis was carried out with FMRIB’s Software Library (FSL; <http://www.fmrib.ox.ac.uk/fsl>). EPI data were preprocessed using a standard stream, including brain extraction, slice-timing correction, motion correction with a six-parameter, rigid-body transformation algorithm, and spatial smoothing with a 8 mm full width at half maximum Gaussian filter. Serial correlations were removed by fitting the data to an autoregressive AR(1) model with pre-whitening, and task-related BOLD signal changes were analyzed according to the general linear model (GLM) in FSL’s fMRI Expert Analysis Tool (FEAT) version 5.98. Separate covariates were created for encoding, delay, and

probe periods of correct and incorrect trials from each condition and convolved with the canonical hemodynamic response function (HRF) for a maximum of eighteen task regressors for each fMRI block. Encoding periods included the 1.5 s instruction slide + 10.5 s stimulus presentation for a total of 12s. The 1.5 s instruction slide was included in order to capture preparatory activity. In order to minimize contamination of delay activity with encoding and probe effects, the delay period was modeled as the middle four seconds between encoding and test [45,46]. The probe period included the 2 s presentation of the test stimulus. Six motion parameters were added as covariates of no interest. To identify brain activation related to the temporal or item demands of the WM task, encoding + delay periods of correct trials were contrasted between conditions. The resulting voxelwise parameter estimate maps were normalized to the MNI152 template using FSL’s Linear Image Registration Tool (FLIRT) in a two-step registration process via the brain-extracted MPRAGE image, combined across fMRI blocks using fixed-effects within-subjects analysis, and entered into mixed-effects group-level analysis. Z (Gaussianised T) statistic images were thresholded using clusters determined by  $Z > 3.09$  ( $p < 0.001$ ) and a family-wise error (FWE) corrected cluster significance threshold of  $p_{FWE} < 0.001$  [47]. Time courses of activation were extracted from the peak voxel in each region that survived FWE cluster corrections.

## 3. Results

### 3.1. WM performance

Overall accuracy on the WM task was high for Item (average = 83.6% correct  $\pm$  2.5 SEM), Group (average = 85.1% correct  $\pm$  1.6 SEM), and Position (average = 80.7% correct  $\pm$  2.9 SEM) trials. Importantly, there were no significant differences in performance across conditions (ANOVA:  $F [2,48] = 0.87$ ;  $p = 0.42$ ). As with performance, reaction times (RT) were also similar between Item (average = 1.2s  $\pm$  0.026 SEM), Group (average = 1.1s  $\pm$  0.028 SEM), and Position (average = 1.1s  $\pm$  0.033 SEM) trials, and no significant differences between trial types were observed (ANOVA:  $F [2,48] = 1.89$ ;  $p = 0.16$ ). These findings indicate that overall engagement and task difficulty, as measured by accuracy and RT, was matched across the conditions.



**Fig. 2.** Regions showing differential activity between Item and Temporal trials. A. Regions showing enhanced activation during Temporal trials (Group + Position trials) relative to Item trials. This contrast identified suprathreshold voxels in DLPFC, posterior parietal cortex, posterior hippocampus and PRC. B. Regions showing enhanced activation during Item trials relative to Temporal trials (Group + Position trials). This contrast identified suprathreshold voxels in medial and anterior PFC, retrosplenial cortex, anterior hippocampus, and PHC. Please see online version of the article for a color figure.

**Table 1**  
Locations of peak voxels across all comparisons.

| Regional local maxima          | Left Hemisphere Voxels<br>Local Maximum (MNI) |     |     |         | Right Hemisphere Voxels<br>Local Maximum (MNI) |     |     |         |
|--------------------------------|---|-----|-----|---------|--|-----|-----|---------|
|                                | X   | Y   | Z   | z-score | X  | Y   | Z   | z-score |
| Temporal > Item                |   |     |     |         |  |     |     |         |
| Dorsolateral Prefrontal Cortex | -42   | 2   | 28  | 27.6    | 36   | 44  | 22  | 19.3    |
| Perirhinal Cortex              | -30   | -2  | -40 | 8.69    | 32   | -4  | -40 | 10.3    |
| Posterior Hippocampus          | -22   | -32 | -4  | 7.1     | 24   | -34 | -2  | 9.19    |
| Posterior Parietal Cortex      | -32   | -52 | 36  | 30.7    | 32   | -58 | 40  | 25.9    |
| Item > Temporal                |   |     |     |         |  |     |     |         |
| Medial Prefrontal Cortex       | -2  | 50  | -6  | 19.4    | 4  | 52  | -2  | 19.6    |
| Parahippocampal Cortex         | -26   | -42 | -16 | 12.6    | 26   | -44 | -10 | 4.15    |
| Anterior Hippocampus           | -24   | -20 | -22 | 6.05    | 26   | -18 | -20 | 5.47    |
| Retrosplenial Cortex           | -8  | -56 | 20  | 20.1    | 10   | -52 | 24  | 15.3    |
| Position > Group               |   |     |     |         |  |     |     |         |
| Posterior Parietal Cortex      | -46   | -60 | 54  | 4.73    | 38   | -50 | 35  | 5.05    |

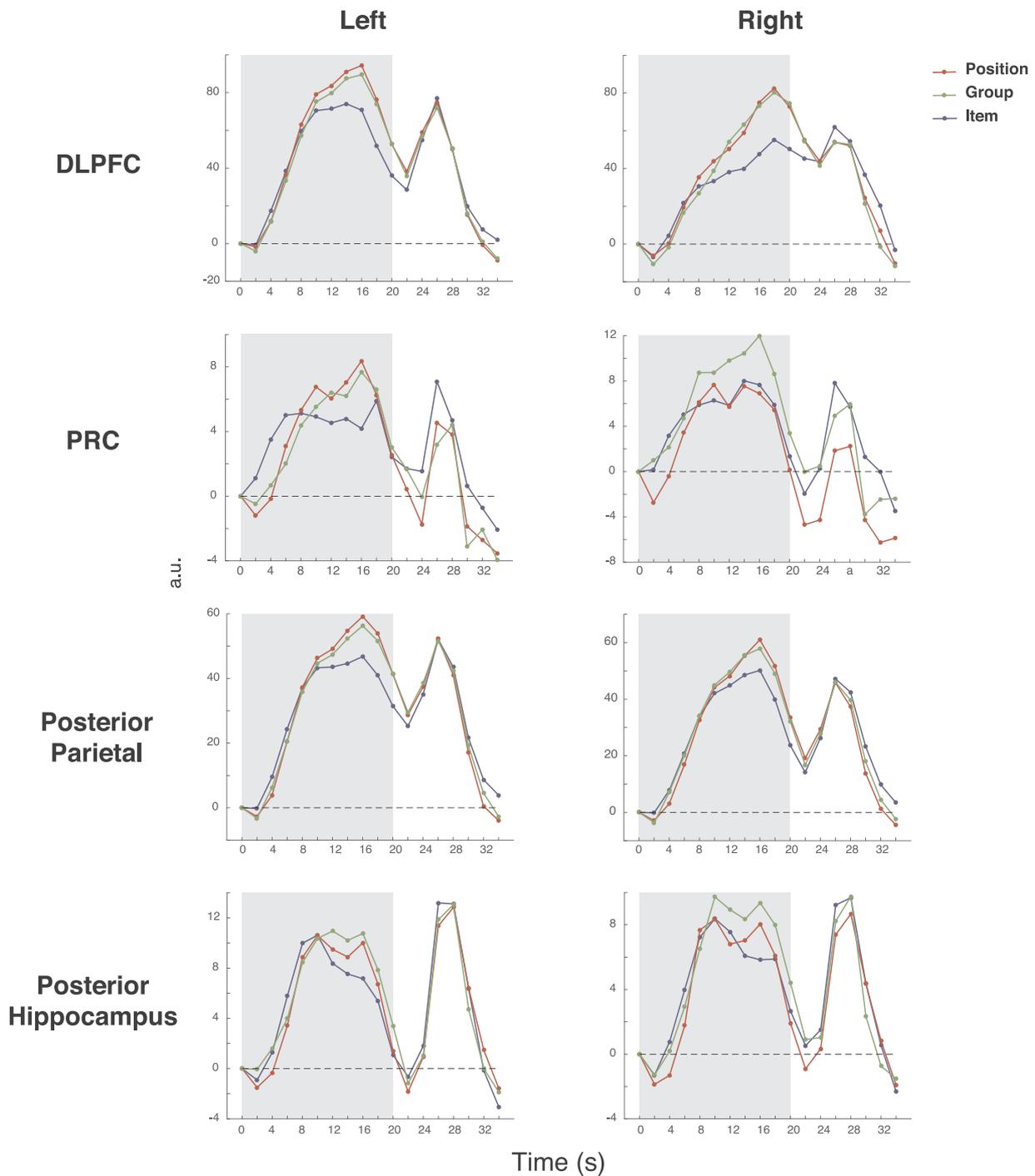
### 3.2. fMRI analysis

To assess activity that was selective to successful temporal WM processes, summed activation across encoding and maintenance periods for correct Temporal trials (Group and Position) was contrasted against encoding and maintenance of correct Item trials. We predicted that activation in DLPFC and posterior parietal cortex would be increased during encoding and maintenance of the temporal order of objects, over and above activation related to encoding and maintenance of object details. Based on work indicating a role for the hippocampus in memory for temporal sequences [29,30,34,48,36], we also predicted that activity in the hippocampus would be enhanced during encoding and maintenance of temporal order information relative to maintenance of visual object features. In particular, we expected this effect to be specific to the posterior hippocampus, given its connectivity with a posterior medial cortical areas involved in representing spatial and temporal information [39]. In contrast, we expected that anterior

hippocampal activity might be increased during Item trials relative to Group and Position trials given its affiliation with PRC and other anterior temporal regions involved in processing of high-level object information [39] and discriminating complex objects [49,50].

Consistent with these predictions, activation in DLPFC, posterior parietal cortex, and the posterior hippocampus was enhanced during the encoding and maintenance phases of Temporal WM trials compared to Item trials (Fig. 2A). Local maxima are indicated in Table 1. In addition, this contrast revealed increased activation in bilateral visual cortex, and left ventrolateral PFC, as well as differences in PRC. Time courses extracted from the peak voxel in each region display a similar pattern of results across regions (Fig. 3)

For the reverse comparison probing greater activation during Item trials compared to Temporal trials, we observed increased activation in bilateral anterior hippocampus, parahippocampal cortex, medial and anterior PFC, and retrosplenial cortex (Fig. 2B). Extracted time courses of activation reveal deactivations across both Temporal conditions, as



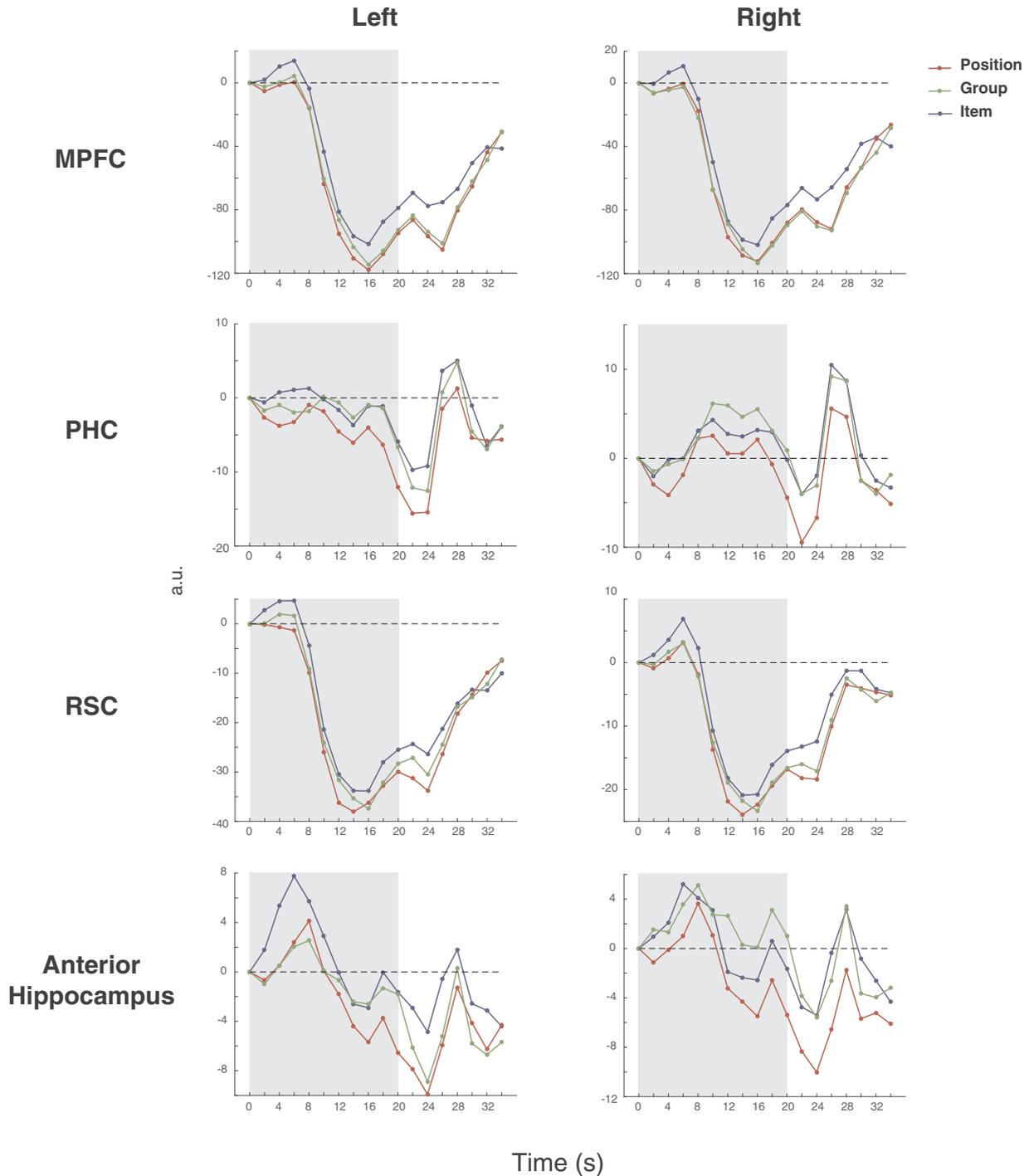
**Fig. 3.** Temporal > Item trials. Time course of activation in regions that exhibited more activity for WM encoding and maintenance of Temporal (Position + Group) trials relative to Item trials. Time periods corresponding to WM encoding and maintenance are shadowed in grey. Please see online version of the article for a color figure.

well as Item trials (Fig. 4).

In order to assess the regions involved in supporting active maintenance of hierarchically organized temporal information across different timescales, activation associated with correct coarse (Group) and fine (Position) temporal trials was contrasted. This analysis revealed increased activation in posterior parietal cortex during fine-grained Position trials, relative to coarse Group trials (Fig. 5). No significant voxels were detected for the reverse comparison (Group vs. Position trials).

#### 4. Discussion

In order to assess the broader circuitry involved in temporal and object WM, the present investigation assessed neural activation in a task where participants were required to actively maintain temporal or visual information across a delay period. Importantly, the number of to-be-maintained items was equivalent across conditions, and both performance and RTs were matched across trial types. Results revealed that, relative to an object WM task, maintenance of temporal WM information was associated with increased activation in the posterior hippocampus, DLPFC, and posterior parietal cortex. Conversely, the



**Fig. 4.** Item > Temporal trials. Time course of activation in regions that exhibited more activity for WM encoding and maintenance of Item trials relative to Temporal (Position + Group) trials. Time periods corresponding to WM encoding and maintenance are shadowed in grey. Please see online version of the article for a color figure.

anterior hippocampus, PHc, medial and anterior PFC and retrosplenial cortex displayed more activation for encoding and WM maintenance of visual item details. In addition to elucidating the broader neural basis for selective temporal and item WM processes, these results suggest a dissociation in the type of WM information maintained across the long axis of the hippocampus. Results also revealed that trials requiring maintenance of fine temporal information were associated with posterior parietal activation relative to maintenance of temporal information at a more coarse scale.

#### 4.1. WM encoding and maintenance of temporal information

The results of the present investigation are consistent with several studies that have demonstrated roles for the PFC and hippocampus in jointly supporting memory for temporal sequences. Work in rodents has shown that disconnection of the hippocampus from the PFC impairs temporal order memory, while sparing object recognition memory [51]. Furthermore, [52] showed that rats with neonatal lesions of hippocampus were impaired on a 4-object serial order task known to rely upon the DLPFC, suggesting that early lesions of the hippocampus can

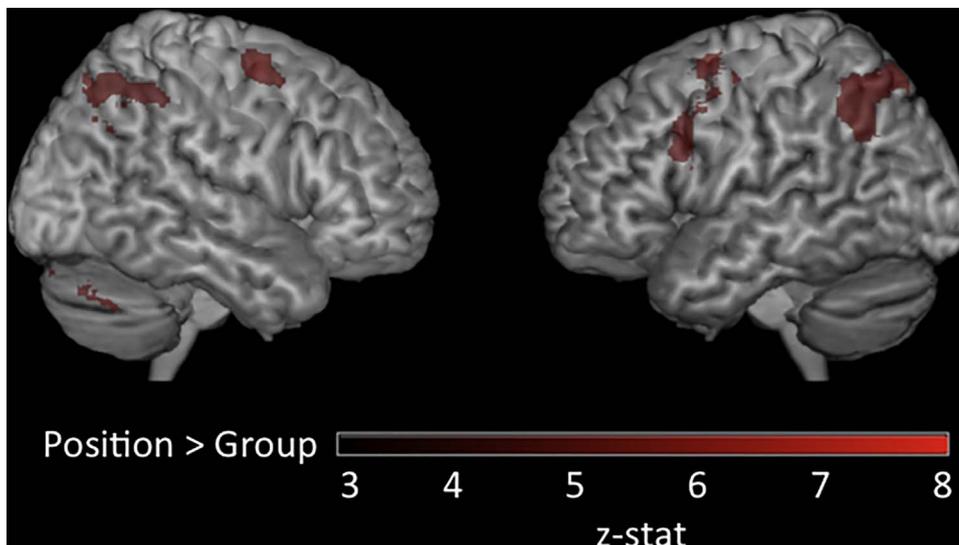


Fig. 5. Regions showing increased activation during Position trials than during Group trials. This contrast revealed suprathreshold activity in posterior parietal cortex. Please see online version of the article for a color figure.

impair the function of the DLPFC, along with hippocampal-DLPFC interactions. Interestingly, we observed a differentiation along the longitudinal axis of the hippocampus, such that posterior regions showed enhanced activation during Temporal trials relative to Item trials. These results provide a link between human neuroimaging and rodent work, where lesions to dorsal hippocampus (homologous to the posterior hippocampus in humans) are associated with an impaired ability to separate events in time ([80,30,29]).

Our results are also consistent with prior fMRI studies demonstrating increased DLPFC and posterior parietal activation during WM trials that required the maintenance of temporal order [53,26,54,55]. These results are also consistent with single-unit recordings in non-human primates that have shown that prefrontal neurons selectively code for objects based in their temporal position within a sequence [23,56,22]. Prefrontal lesions in nonhuman primates [57] have also revealed impaired performance on a self-ordered serial order task, while memory for the stimuli remained intact. Similarly, lesion studies in rodents that have demonstrated impairments in memory for sequences of objects [58,59], spatial locations [60,61,17], or odors [62] following damage to the PFC. These findings suggest that an intact fronto-parietal network is necessary for the maintenance of temporal sequences.

Surprisingly, we found increased PRC activation during Temporal trials relative to Item trials. Although these results seem to be contrary to work suggesting that PRC is important for fine-grained object perception [49,50], they align with studies in rodents [63,58,64] and nonhuman primates [65–67] that have identified a critical role for the PRC in memory for object sequences. For example, bilateral inactivation (using a sodium channel blocker) of PRC or crossed unilateral inactivation of PRC and PFC significantly impaired memory for sequences of objects [63]. Furthermore, single-unit recordings in monkeys have shown the PRC and hippocampus interact during temporal memory, with the hippocampus providing incremental timing signals during stimulus presentation, and the PRC integrating timing information from the hippocampus with item information from visual regions [67].

To our knowledge, our study provides the first evidence from human imaging studies demonstrating involvement of the PRC in temporal WM. Taken together, the data indicate that the DLPFC, posterior hippocampus, and PRC collectively contribute to the online maintenance of temporal sequences.

#### 4.2. WM encoding and maintenance of visual information

A number of regions, including the anterior hippocampus, PHC,

medial and anterior PFC, and retrosplenial cortex showed enhanced activation during Item trials relative to Temporal trials. Given that these regions are not typically associated with object processing, it is interesting to consider why they exhibited increased activity during Item trials relative to Temporal trials. One explanation is that involvement of the anterior hippocampus, medial PFC, and retrosplenial cortex reflects repeated recollection of visual details of the presented stimuli in order to facilitate probe performance. This alternative account stems from the fact that foil items presented during the Item probe were very visually similar to the items presented during encoding. In order to correctly respond during the probe, access to detailed information about the visual features of presented items is required, and may have been continually recollected over the course of the trial. This explanation is admittedly speculative, but it is consistent with work showing that activity in the anterior hippocampus is enhanced active maintenance of novel visual objects [45,68,69], and with the idea that the medial PFC and retrosplenial cortex are associated with a “core recollection network” that is reliably engaged during recollection of recent events [70].

Another interpretation of these results is that they reflect selective deactivation in the default-mode network for Temporal relative to Item trials, reflecting increased mind wandering during this condition [71]. A number of results suggest that this explanation does not account for the present results. First, although the posterior hippocampus is often considered as part of the default network [72,73], this region displayed *increased* activation during Temporal trials relative to Item trials. Additionally, extracted time courses show a common pattern of deactivation across conditions, arguing against the idea that default-mode network regions were selectively disengaged during Temporal trials. Performance and reaction time data also do not support the idea that Item trials were less cognitively demanding than Temporal trials (see Results section).

Finally, it is possible that the difference in mPFC and retrosplenial cortex activity between Item and Temporal trials is related to differences in low frequency oscillatory activity that sometimes result in reductions in BOLD signal. Previous EEG studies have indicated that the power of frontal theta oscillations is increased during maintenance of temporal sequences relative to maintenance of object details [24,25]. Results from fMRI studies indicate that increased theta activity may be associated with reduced BOLD signal in regions that include medial PFC, retrosplenial, and posterior cingulate cortex [81,82], particularly during WM tasks [74,75]. Thus it is possible that deactivation in medial PFC, retrosplenial cortex, PHC, and anterior hippocampus is indicative of theta activity which plays a role in WM for sequence information

[24,25]. Further studies, using simultaneous recordings of EEG and fMRI data, will be needed to test this hypothesis.

#### 4.3. Temporal WM across timescales

Our final analysis addressed the question of how the active maintenance of hierarchically organized temporal information varies across different timescales. To investigate this question, neural activity associated with WM maintenance of fine temporal information (Position trials) was compared against activity associated with WM maintenance of coarse temporal information (Group trials). Results indicated that Position trials were characterized by increased activation in posterior parietal cortex, suggesting that this region is particularly involved in maintaining more detailed temporal information in WM. Given that both accuracy and RTs were matched across Position and Group trials, it is unlikely that these effects can be explained by differences in difficulty.

#### 5. Conclusion

The present results provide evidence for the involvement of a broad network of regions in supporting temporal WM. Maintenance of temporal WM information engages the DLPFC as well as regions in the MTL, including the posterior hippocampus and bilateral PRC. This investigation also indicates a key role for the posterior parietal cortex in the online maintenance of temporal information during goal-guided behavior, with the strongest effects present across temporal information at more fine timescales in hierarchically organized temporal sequences.

In addition to shedding light on the broad network of regions involved in temporal WM, the present investigation also provides evidence for WM specialization along the longitudinal axis of the hippocampus. Specifically, whereas posterior hippocampal activity was enhanced during maintenance of temporal order, anterior hippocampal activation was enhanced during maintenance of detailed visual object information. Taken together, the present findings provide a foundation for future investigations to probe the kinds of information encoded by prefrontal, parietal, and medial temporal lobe regions (cf. [34,76]), and how these regions interact (cf. [77]) during maintenance of temporal sequences.

#### Acknowledgements

This work was funded by NIMH grant R01MH068721 and a Guggenheim Fellowship to C.R., and an NSF Graduate Research Fellowship to M.C.I. (#1148897).

#### References

[1] N. Cowan, Activation, attention, and short-term memory, *Mem. Cognit.* 21 (2) (1993) 162–167.

[2] M. D'Esposito, B.R. Postle, The cognitive neuroscience of working memory, *Annu. Rev. Psychol.* 66 (2015) 115–142, <http://dx.doi.org/10.1146/annurev-psych-010814-015031> (Epub 012014 Sep 010819).

[3] J. Quintana, J.M. Fuster, From perception to action: temporal integrative functions of prefrontal and parietal neurons, *Cereb. Cortex* 9 (3) (1999) 213–221.

[4] J.M. Fuster, The prefrontal cortex—an update: time is of the essence, *Neuron* 30 (2) (2001) 319–333.

[5] J.M. Fuster, Upper processing stages of the perception-action cycle, *Trends Cogn. Sci.* 8 (4) (2004) 143–145.

[6] J.M. Fuster, The cognit: a network model of cortical representation, *Int. J. Psychophysiol.* 60 (2) (2006) 125–132 (Epub 2006 Apr 2019).

[7] J.M. Fuster, Cortex and memory: emergence of a new paradigm, *J. Cogn. Neurosci.* 21 (11) (2009) 2047–2072 (2010.1162/jocn.2009.21280).

[8] J.M. Fuster, S.L. Bressler, Cognit activation: a mechanism enabling temporal integration in working memory, *Trends Cogn. Sci.* 16 (4) (2012) 207–218 (210.1016/j.tics.2012.1003.1005. Epub 2012 Mar 1020).

[9] T.B. Christophel, P.C. Klink, B. Spitzer, P.R. Roelfsema, J.-D. Haynes, The distributed nature of working memory, *Trends Cogn. Sci.* (2017), <http://dx.doi.org/10.1016/j.tics.2016.12.007>.

[10] A.D. Baddeley, Verbal and visual subsystems of working memory, *Curr. Biol.* 3 (8) (1993) 563–565.

[11] N. Burgess, G. Hitch, Memory for serial order: a network model of the phonological loop and its timing, *Psychol. Rev.* 106 (3) (1999) 551–581.

[12] R.N. Henson, Positional information in short-term memory: relative or absolute? *Mem. Cognit.* 27 (5) (1999) 915–927.

[13] G.D. Brown, T. Preece, C. Hulme, Oscillator-based memory for serial order, *Psychol. Rev.* 107 (1) (2000) 127–181.

[14] B.R. Postle, Working memory as an emergent property of the mind and brain, *Neuroscience* 139 (1) (2006) 23–38 (Epub 2005 Dec 2001).

[15] A.P. Shimamura, J.S. Janowsky, L.R. Squire, Memory for the temporal order of events in patients with frontal lobe lesions and amnesic patients, *Neuropsychologia* 28 (8) (1990) 803–813.

[16] M.P. McAndrews, B. Milner, The frontal cortex and memory for temporal order, *Neuropsychologia* 29 (9) (1991) 849–859.

[17] R.P. Kesner, R.O. Hopkins, B. Fineman, Item and order dissociation in humans with prefrontal cortex damage, *Neuropsychologia* 32 (8) (1994) 881–891.

[18] R. Cabeza, J. Mangels, L. Nyberg, R. Habib, S. Houle, A.R. McIntosh, E. Tulving, Brain regions differentially involved in remembering what and when: a PET study, *Neuron* 19 (4) (1997) 863–870.

[19] R. Cabeza, N.D. Anderson, S. Houle, J.A. Mangels, L. Nyberg, Age-related differences in neural activity during item and temporal-order memory retrieval: a positron emission tomography study, *J. Cogn. Neurosci.* 12 (1) (2000) 197–206.

[20] L.J. Jenkins, C. Ranganath, Prefrontal and medial temporal lobe activity at encoding predicts temporal context memory, *J. Neurosci.* 30 (46) (2010) 15558–15565 (15510.11523/JNEUROSCI.11337-15510.12010).

[21] S. Tubridy, L. Davachi, Medial temporal lobe contributions to episodic sequence encoding, *Cereb. Cortex* 21 (2) (2011) 272–280 (210.1093/cercor/bhq1092. Epub 2010 May 1021).

[22] Y. Ninokura, H. Mushiaki, J. Tanji, Integration of temporal order and object information in the monkey lateral prefrontal cortex, *J. Neurophysiol.* 91 (1) (2004) 555–560 (Epub 2003 Sep 2010).

[23] S. Funahashi, M. Inoue, K. Kubota, Delay-period activity in the primate prefrontal cortex encoding multiple spatial positions and their order of presentation, *Behav. Brain Res.* 84 (1–2) (1997) 203–223.

[24] L.T. Hsieh, A.D. Ekstrom, C. Ranganath, Neural oscillations associated with item and temporal order maintenance in working memory, *J. Neurosci.* 31 (30) (2011) 10803–10810 (10810.11523/JNEUROSCI.10828-10811.12011).

[25] B.M. Roberts, L.T. Hsieh, C. Ranganath, Oscillatory activity during maintenance of spatial and temporal information in working memory, *Neuropsychologia* 51 (2) (2013) 349–357 (310.1016/j.neuropsychologia.2012.1010.1009. Epub 2012 Oct 1016).

[26] C. Marshuetz, E.E. Smith, Working memory for order information: multiple cognitive and neural mechanisms, *Neuroscience* 139 (1) (2006) 195–200 (Epub 2005 Dec 2015).

[27] L. Attout, W. Fias, E. Salmon, S. Majerus, Common neural substrates for ordinal representation in short-term memory, numerical and alphabetical cognition, *PLoS One* 9 (3) (2014) e92049 (92010.91371/journal.pone.0092049. eCollection 0092014).

[28] S. Majerus, A. D'Argembeau, T. Martinez Perez, S. Belayachi, M. Van der Linden, F. Collette, E. Salmon, R. Seurinck, W. Fias, P. Maquet, The commonality of neural networks for verbal and visual short-term memory, *J. Cogn. Neurosci.* 22 (11) (2010) 2570–2593 (2510.1162/jocn.2009.21378).

[29] N.J. Fortin, K.L. Agster, H.B. Eichenbaum, Critical role of the hippocampus in memory for sequences of events, *Nat. Neurosci.* 5 (5) (2002) 458–462.

[30] R.P. Kesner, P.E. Gilbert, L.A. Barua, The role of the hippocampus in memory for the temporal order of a sequence of odors, *Behav. Neurosci.* 116 (2) (2002) 286–290.

[31] R.O. Hopkins, R.P. Kesner, Item and order recognition memory in subjects with hypoxic brain injury, *Brain Cogn.* 27 (1995) 180.

[32] A.R. Mayes, C.L. Isaac, J.S. Holdstock, N.M. Hunkin, D. Montaldi, J.J. Downes, Formation in working memory: fMRI evidence for parietal and prefrontal mechanisms. resonance imaging study. tion Functional Imaging. Tepad lesions, *Cogn. Neuropsychol.* (2001) 18 (97ve Neuropsychology., Holdstock, J.S. Hunki).

[33] J. Madsen, R.P. Kesner, The temporal-distance effect in subjects with dementia of the Alzheimer type, *Alzheimer Dis. Assoc. Disord.* 9 (2) (1995) 94.

[34] L.T. Hsieh, M.J. Gruber, L.J. Jenkins, C. Ranganath, Hippocampal activity patterns carry information about objects in temporal context, *Neuron* 81 (5) (2014) 1165–1178 (1110.1016/j.neuron.2014.1101.1015).

[35] K. Kalm, M.H. Davis, D. Norris, Individual sequence representations in the medial temporal lobe, *J. Cogn. Neurosci.* 25 (7) (2013) 1111–1121 (1110.1162/jocn\_a\_00378. Epub 02013 Feb 00328).

[36] L.J. Jenkins, C. Ranganath, Distinct neural mechanisms for remembering when an event occurred: dual Mechanisms for Recency Discrimination, *Hippocampus* 26 (5) (2016) 554–559, <http://dx.doi.org/10.1002/hipo.22571>.

[37] C. Ranganath, L.-T. Hsieh, The hippocampus: a special place for time: the hippocampus: a special place for time, *Ann. N. Y. Acad. Sci.* 1369 (1) (2016) 93–110, <http://dx.doi.org/10.1111/nyas.13043>.

[38] I. Kahn, J.R. Andrews-Hanna, J.L. Vincent, A.Z. Snyder, R.L. Buckner, Distinct cortical anatomy linked to subregions of the medial temporal lobe revealed by intrinsic functional connectivity, *J. Neurophysiol.* 100 (1) (2008) 129, <http://dx.doi.org/10.1152/jn.00077.2008>.

[39] L.A. Libby, A.D. Ekstrom, J.D. Ragland, C. Ranganath, Differential connectivity of perirhinal and parahippocampal cortices within human hippocampal subregions revealed by high-resolution functional imaging, *J. Neurosci.* 32 (19) (2012) 6550, <http://dx.doi.org/10.1523/jneurosci.3711-11.2012>.

[40] J. Poppenk, H.R. Eversmoen, M. Moscovitch, L. Nadel, Long-axis specialization of the human hippocampus, *Trends Cogn. Sci.* 17 (5) (2013) 230–240, <http://dx.doi.org/10.1016/j.tics.2013.03.005>.

- [41] J. Ryan, Grouping and short-term memory: different means and patterns of grouping, *Q. J. Exp. Psychol.* 21 (2) (1969) 137–147.
- [42] J. Ryan, Temporal grouping, rehearsal and short-term memory, *Q. J. Exp. Psychol.* 21 (2) (1969) 148–155.
- [43] K. Kalm, M.H. Davis, D. Norris, Neural mechanisms underlying the grouping effect in short-term memory, *Hum. Brain Mapp.* 33 (7) (2012) 1634–1647 (1610.1002/hbm.21308. Epub 22011 Jul 21307).
- [44] J.L. Voss, C.L. Baym, K.A. Paller, Accurate forced-choice recognition without awareness of memory retrieval, *Learn. Mem.* 15 (6) (2008) 454–459 (410.1101/lm.971208. Print 972008 Jun.).
- [45] C. Ranganath, M. D'Esposito, Medial temporal lobe activity associated with active maintenance of novel information, *Neuron* 31 (5) (2001) 865–873.
- [46] C. Ranganath, A. Heller, M.X. Cohen, C.J. Brozinsky, J. Rissman, Functional connectivity with the hippocampus during successful memory formation, *Hippocampus* 15 (8) (2005) 997–1005.
- [47] K.J. Worsley, Statistical analysis of activation images, in: P. Jezzard, P.M. Matthews, S.M. Smith (Eds.), *Functional MRI: An Introduction to Methods*, 2001 (Ch 14).
- [48] S. DuBrow, L. Davachi, Temporal binding within and across events, *Neurobiol. Learn. Mem.* 134 (2016) 107–114, <http://dx.doi.org/10.1016/j.nlm.2016.07.011>.
- [49] M.D. Barense, D. Gaffan, K.S. Graham, The human medial temporal lobe processes online representations of complex objects, *Neuropsychologia* 45 (13) (2007) 2963–2974 (Epub 2007 Jun 2914).
- [50] M.E. Mundy, P.E. Downing, D.M. Dwyer, R.C. Honey, K.S. Graham, A critical role for the hippocampus and perirhinal cortex in perceptual learning of scenes and faces: complementary findings from amnesia and fMRI, *J. Neurosci.* 33 (25) (2013) 10490–10502 (10410.11523/JNEUROSCI.12958-10412.12013).
- [51] G.R. Barker, E.C. Warburton, When is the hippocampus involved in recognition memory? *J. Neurosci.* 31 (29) (2011) 10721–10731 (10710.11523/JNEUROSCI.16413-10710.12011).
- [52] E. Heuer, J. Bachevalier, Working memory for temporal order is impaired after selective neonatal hippocampal lesions in adult rhesus macaques, *Behav Brain Res.* 239 (2013) 55–62, <http://dx.doi.org/10.1016/j.bbr.2012.10.1043> (Epub 2012 Nov 1015).
- [53] C. Marshuetz, E.E. Smith, J. Jonides, J. DeGutis, T.L. Chenevert, Order information in working memory: fMRI evidence for parietal and prefrontal mechanisms, *J. Cogn. Neurosci.* 12 (Suppl. 2) (2000) 130–144.
- [54] C. Marshuetz, P.A. Reuter-Lorenz, E.E. Smith, J. Jonides, D.C. Noll, Working memory for order and the parietal cortex: an event-related functional magnetic resonance imaging study, *Neuroscience* 139 (1) (2006) 311–316 (Epub 2006 Jan 2018).
- [55] C. Amiez, M. Petrides, Selective involvement of the mid-dorsolateral prefrontal cortex in the coding of the serial order of visual stimuli in working memory, *Proc. Natl. Acad. Sci. U. S. A.* 104 (34) (2007) 13786–13791 (Epub 12007 Aug 13715).
- [56] Y. Ninokura, H. Mushiaki, J. Tanji, Representation of the temporal order of visual objects in the primate lateral prefrontal cortex, *J. Neurophysiol.* 89 (5) (2003) 2868–2873.
- [57] M. Petrides, Functional specialization within the dorsolateral frontal cortex for serial order memory, *Proc. Biol. Sci.* 246 (1317) (1991) 299–306.
- [58] G.R. Barker, F. Bird, V. Alexander, E.C. Warburton, Recognition memory for objects, place, and temporal order: a disconnection analysis of the role of the medial prefrontal cortex and perirhinal cortex, *J. Neurosci.* 27 (11) (2007) 2948–2957.
- [59] J.B. Mitchell, J. Laiacona, The medial frontal cortex and temporal memory: tests using spontaneous exploratory behaviour in the rat, *Behav. Brain Res.* 97 (1–2) (1998) 107–113.
- [60] A.A. Chiba, R.P. Kesner, A.M. Reynolds, Memory for spatial location as a function of temporal lag in rats: role of hippocampus and medial prefrontal cortex, *Behav. Neural Biol.* 61 (2) (1994) 123–131.
- [61] R.P. Kesner, T. Holbrook, Dissociation of item and order spatial memory in rats following medial prefrontal cortex lesions, *Neuropsychologia* 25 (4) (1987) 653–664.
- [62] L.M. Devito, H. Eichenbaum, Memory for the order of events in specific sequences: contributions of the hippocampus and medial prefrontal cortex, *J. Neurosci.* 31 (9) (2011) 3169–3175 (3110.1523/JNEUROSCI.4202-3110.2011).
- [63] D.K. Hansson, J.G. Howland, A.G. Phillips, Interaction between perirhinal and medial prefrontal cortex is required for temporal order but not recognition memory for objects in rats, *J. Neurosci.* 24 (19) (2004) 4596–4604.
- [64] E.C. Warburton, M.W. Brown, Findings from animals concerning when interactions between perirhinal cortex, hippocampus and medial prefrontal cortex are necessary for recognition memory, *Neuropsychologia* 48 (8) (2010) 2262–2272 (2210.1016/j.neuropsychologia.2009.2212.2022. Epub 2009 Dec 2221).
- [65] F.L. Fahy, I.P. Riches, M.W. Brown, Neuronal activity related to visual recognition memory: long-term memory and the encoding of recency and familiarity information in the primate anterior and medial inferior temporal and rhinal cortex, *Exp. Brain Res.* 96 (3) (1993) 457–472.
- [66] S.R. Lehky, K. Tanaka, Enhancement of object representations in primate perirhinal cortex during a visual working-memory task, *J. Neurophysiol.* 97 (2) (2007) 1298–1310 (Epub 2006 Nov 1215).
- [67] Y. Naya, W.A. Suzuki, Integrating what and when across the primate medial temporal lobe, *Science* 333 (6043) (2011) 773–776 (710.1126/science.1206773).
- [68] E.A. Nichols, Y.C. Kao, M. Verfaellie, J.D. Gabrieli, Working memory and long-term memory for faces: evidence from fMRI and global amnesia for involvement of the medial temporal lobes, *Hippocampus* 16 (7) (2006) 604–616.
- [69] R.K. Olsen, E.A. Nichols, J. Chen, J.F. Hunt, G.H. Glover, J.D. Gabrieli, A.D. Wagner, Performance-related sustained and anticipatory activity in human medial temporal lobe during delayed match-to-sample, *J. Neurosci.* 29 (38) (2009) 11880–11890 (11810.11523/JNEUROSCI.12245-11809.12009).
- [70] M.D. Rugg, K.L. Vilberg, Brain networks underlying episodic memory retrieval, *Curr. Opin. Neurobiol.* 23 (2) (2013) 255–260 (210.1016/j.conb.2012.10.11.1005. Epub 2012 Dec 1011).
- [71] M.E. Raichle, A.M. MacLeod, A.Z. Snyder, W.J. Powers, D.A. Gusnard, G.L. Shulman, A default mode of brain function, *Proc. Natl. Acad. Sci. U. S. A.* 98 (2) (2001) 676–682.
- [72] J.L. Vincent, A.Z. Snyder, M.D. Fox, B.J. Shannon, J.R. Andrews, M.E. Raichle, R.L. Buckner, Coherent spontaneous activity identifies a hippocampal-parietal memory network, *J. Neurophysiol.* 96 (6) (2006) 3517–3531 (Epub 2006 Aug 3519).
- [73] M.D. Fox, M.E. Raichle, Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging, *Nat. Rev. Neurosci.* 8 (9) (2007) 700–711.
- [74] R. Scheeringa, K.M. Petersson, R. Oostenveld, D.G. Norris, P. Hagoort, M.C. Bastiaansen, Trial-by-trial coupling between EEG and BOLD identifies networks related to alpha and theta EEG power increases during working memory maintenance, *Neuroimage* 44 (3) (2009) 1224–1238 (1210.1016/j.neuroimage.2008.1208.1041. Epub 2008 Sep 1218).
- [75] J.A. Meltzer, M. Negishi, L.C. Mayes, R.T. Constable, Individual differences in EEG theta and alpha dynamics during working memory correlate with fMRI responses across subjects, *Clin. Neurophysiol.* 118 (11) (2007) 2419–2436 (Epub 2007 Sep 2427).
- [76] L.-T. Hsieh, C. Ranganath, Cortical and subcortical contributions to sequence retrieval: schematic coding of temporal context in the neocortical recollection network, *NeuroImage* 121 (2015) 78–90, <http://dx.doi.org/10.1016/j.neuroimage.2015.07.040>.
- [77] A.M. Schedlbauer, M.S. Copara, A.J. Watrous, A.D. Ekstrom, Multiple interacting brain areas underlie successful spatiotemporal memory retrieval in humans, *Sci. Rep.* 4 (2014) 6431, <http://dx.doi.org/10.1038/srep06431>.
- [78] E. Heuer, J. Bachevalier, Working memory for temporal order is impaired after selective neonatal hippocampal lesions in adult rhesus macaques, *Behav. Brain Res.* 239 (2013) 55–62.
- [79] C. Marshuetz, E.E. Smith, J. Jonides, J. DeGutis, T.L. Chenevert, Order information in working memory: fMRI evidence for parietal and prefrontal mechanisms, *J. Cogn. Neurosci.* (2000).
- [80] R.P. Kesner, M.R. Hunsaker, The temporal attributes of episodic memory, *Behav. Brain Res.* 215 (2) (2010) 299–309.
- [81] L.-T. Hsieh, C. Ranganath, Frontal midline theta oscillations during working memory maintenance and episodic encoding and retrieval, *Neuroimage* 85 (2014) 721–729.
- [82] R. Scheeringa, M.C.M. Bastiaansen, K.M. Petersson, R. Oostenveld, P. Hagoort, Frontal theta EEG activity correlates negatively with the default mode network in resting state, *Int. J. Psychophysiol.* 67 (3) (2008) 242–251.