Winter 12-1-2012

Separating Component Signals of Episodic Simulation Using a Catch Trial Design

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A thesis presented to the
graduate School of Arts and Sciences
of Washington University in
partial fulfillment of the
requirements for the
degree of Master of Arts

December 2012

Saint Louis, Missouri

Abstract

Tasks that require mentally simulating events, such as remembering events from one's past and imagining events from one's future, have been shown to involve a highly overlapping set of brain regions. Across a growing number of studies, relatively few regions have been found that show differences in activity between remembered and imagined events. However, studies have not disambiguated neural activity related to task orientation (i.e., preparing to remember events from the past or imagine events in the future) from activity related simulating events, *per se*. The current experiment uses functional MRI and employs a catch trial design to test the hypothesis that by separating orientation and simulation related activity, novel differences might be found between the acts of remembering and imagining events. We find that regions typically shown to activate above baseline in simulation tasks actually deactivate slightly in response to orientation cues, and that by accounting for this activity, regions in bilateral parahippocampal and right retrosplenial cortex show increased activity for the simulation of past events relative to the simulation of future events. This finding suggests that multiple, temporally overlapping processes exist in regions involved in episodic simulation, and that these differences concealed a network of regions sensitive to situations in which information from one's past is explicitly retrieved.

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Acknowledgments

I would like to thank Kathleen McDermott for her constant advice, encouragement, and support throughout the entirety of this project. I would also like to thank the other members of my committee, Ian Dobbins and Todd Braver, for providing many helpful comments as this work was both conceptualized and carried out. Additionally, I thank Steve Nelson for his technical assistance and thoughtful discussion throughout the project. Andrew Fishell and Neil Savalia were of great assistance with data collection, and I thank them for their time and diligence.

This material is based upon work supported by the National Science Foundation Graduate Research Fellowship under Grant No. DGE-1143954, and a grant from the McDonnell Center for Systems Neuroscience at Washington University in St. Louis (awarded to Kathleen McDermott).

INTRODUCTION

A defining ability of the human mind is the capacity to recall and re-experience memories from one's own past. This ability is thought to be supported by episodic memory, defined as memory for personal experiences, and the specific people, objects, and places associated with these experiences [1; 2]. In addition, it has also been hypothesized that this same memory system is flexible enough to enable humans to mentally travel forward in time to imagine themselves in the future [3], a process known as episodic future thought [4]. A growing body of literature from cognitive psychology, neuropsychology, and cognitive neuroscience has supported the hypothesis that both remembering the past and envisioning the future (or other hypothetical scenarios) rely on highly overlapping neural and cognitive mechanisms (for recent review, see [5]). While originally the concept of autonoetic consciousness was coined to encompass various forms of "mental time travel" [3], more recently the term "episodic simulation" has been invoked to describe projections of the self through time (e.g., [6]), and when speaking of both of these processes collectively, this latter term will be used throughout the rest of this report.

Recent neuroimaging data regarding similarities in remembering and imagining

Over the past half-decade, a number of cognitive neuroscience studies have examined the neural correlates of episodic simulation, primarily using fMRI (e.g., [7; 8]). Research in this area has consistently identified a set of regions that are commonly engaged when one is either recalling events from one's personal past, imagining events that might occur in one's future, or even imagining other hypothetical scenarios (i.e., these regions appear to be commonly engaged by a variety of simulation tasks; see e.g.,

[7-11]). These regions of overlap include ventral and dorsal portions of the medial prefrontal cortex, posterior cingulate cortex (extending into regions of the precuneus and retrosplenial cortex), bilateral superior frontal cortex, bilateral inferior parietal lobule (especially the angular gyrus), and bilateral hippocampal formation (for in-depth discussions and reviews, see [12; 13]).

The finding of largely overlapping regions has been accompanied by another consistent finding, which is a relative *lack* of differences that emerge when one directly compares activity across brain regions for episodic memory and episodic future thought. When such differences are found, research has consistently shown greater BOLD activity for episodic future thought than for remembering episodic events (for review and discussion, see [13]). It has been argued that greater activity related to the envisioning of future events reflects greater processing demands, as various elements must be combined across a number of disparate events, whereas for remembered events only a single, coherent memory trace is activated [7; 8].

Conversely, no regions have been reliably shown to elicit greater activity for remembered events than imagined future events. This relative lack of difference is surprising, especially from the perspective of reality monitoring [14]: events that are imagined are not typically confused with events that occurred in our pasts. Yet the implication from contemporary neuroimaging findings appears to be that the same core regions are engaged, with the biomarker of "remembered" versus "imagined" events being signal strength in these regions (e.g., in left superior frontal gyrus [7] or right hippocampal formation [8]). If overall "mental effort" (as represented by level of activity) within a handful of regions reflects the status of remembered (i.e., 'real') versus

imagined events, one might expect more source confusion than is commonly observed, and therefore this possibility seems unsatisfactory.

Existing neuroimaging approaches have combined task orientation with event simulation

The relatively few differences in activity observed between conditions of remembering and imagining may be attributable to the methods commonly used in episodic simulation research. The studies have used variants of the Galton-Crovitz word cueing technique [15], in which an orientation cue to directs participants to think about either the past or the future, and then a short word or picture "event probe" helps participants form some scenario. Figure 1 includes examples from several recent studies using this basic paradigm (specifically [7; 10]).

A potential limitation to using this approach is that it conflates the BOLD response to the orientation cue and to the event probe, and it seems important that these two components should be separated. It has been hypothesized by Tulving that in order to retrieve information from episodic memory, one must enter a specific cognitive task state, known as retrieval mode [2], and research since then has demonstrated that this preparation to retrieve information evokes a different BOLD response than does the retrieval itself (see e.g., [16]). Cognitive neuroscience studies that have used methodologies summarized in Figure 1 cannot distinguish activity related to entering this mental state from the activity related to simulating experiences, either remembered from the past or imagined in the future. Similarly, to the extent that one might have to enter a "future mode" task set when imagining events that might occur in one's own future, current designs have not allowed a separation of activity orienting toward the future from

activity related specifically to simulation of the future event. It seems necessary to disambiguate these possibly different task sets from the simulation period following each one if we are to properly characterize differences that may exist between retrieving past events and imagining hypothetical future events.

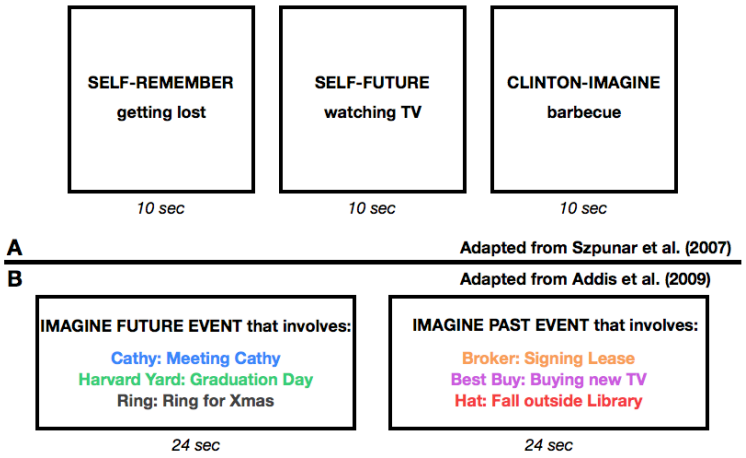

Figure 1. Summary of previous designs of episodic simulation studies. Trialwise instructions consist of simultaneously providing participants with task orientation instructions as well as a probe to help participants simulate an event. Methods described are taken from [7; 10].

It may be the case that differences exist during the orientation component of simulation trials (i.e., when one is adopting a specific task set), during the simulation component, or both. If differences exist in only one or the other component of a given simulation trial, combining both components into a single modeled BOLD response may not provide sufficient power to observe these differences. Furthermore, if one type of trial shows greater activity in response to task orientation, and less activity in response to the event probe, this effect may be "averaged out" by combining these components into a single response. Given these possibilities, separating orientation from event probe simulation components may provide novel insights into differences between the remembering of past events and the envisioning of events from one's future.

Catch trials allow separation of component processes

One means of separating component processes within a given trial is to incorporate a catch trial design [17-19]. This technique involves separating trials into two or more

components. To use the example from Fig. 1a, it might involve providing an orientation cue (e.g., "SELF-REMEMBER") and an event probe to direct a specific simulation (e.g., "getting lost"). On full, or "compound," trials, both trial components are presented. For a small percentage of trials, known as "catch trials", only the initial component (in the current example, "SELF-REMEMBER") is presented, after which point the trial ends. The addition of these catch trials enables separate modeling of orientation cue and event probe components of trials. This separation can provide insights into how orientation-related (or preparatory) activity can impact event probe-related activity (for related discussion, see [16]).

Summary of basic question

The main question we are seeking to answer in the reported experiment is whether novel differences between episodic memory and episodic future thought might be observed when neural activity during these processes is isolated from that activity associated with the orientation cue. By using fMRI and incorporating a catch trial design, we will be able to separately model the orientation and event probe components of trials. We will compare activity for remembered events and imagined future events associated with event probes (i.e., with the act of simulation events per se, rather than orientation as well as simulation), along with activity for a control simulation condition, in which participants are asked to imagine a familiar other (in this case, President Barack Obama) engaging in various activities. We predict that by "off-loading" the orientation-related activity from simulation-related activity, we will be able to detect novel differences in brain areas that typically demonstrate "common" activity between remember and future conditions in previous simulation experiments.

METHODS

Participants

Twenty-eight young adult subjects were recruited from Washington University and the surrounding metro St. Louis area. One subject was excluded from analysis due to excessive movement, one subject was excluded due to a failure to comply with task instructions, and two subjects was eliminated due to a failure to reach criterion performance (see *manipulation check* below). For the remaining 24 subjects (14 female), ages ranged from 18 to 36 years (mean = 23.9). All participants were right-handed, native speakers of English, with normal or corrected-to-normal vision, and no reported history of psychiatric illness. Due to an isolated case of excessive movement, one subject had a single experimental run dropped from analysis. For the remaining 23 subjects, all 3 experimental runs were included.

All participants were consented in accordance with the guidelines set forward by the Human Research Protection Office at Washington University, and were compensated for their time at a rate of $25/hour.

Task stimuli

Stimuli consisted of 90 words and short phrases. These depicted common objects (e.g., board game), locations (e.g., library), and activities (e.g., visiting relatives). Seventy-two of these stimuli were taken from a previous laboratory study [7], and the other stimuli were novel and generated specifically for this experiment. Stimuli ranged in length from 3-22 characters in length (mean = 10.9), and organized into 6 lists of 15 words each that were matched for word length. List order was counterbalanced across participants, and words within each list were randomized for each participant. Across all

participants, words were equally likely to appear in each experimental condition (see below). Since participants only saw 72 of the 90 total stimuli, the items withheld for each participant were counterbalanced such that each word was withheld equally often across all participants. All stimuli, including a fixation cross shown between task trials, were presented to participants in 48-point Arial font.

Simulation task

Figure 2 summarizes the experimental task. Participants performed the experimental task across three functional runs within the fMRI scanner. In each run, participants were presented with a series of 24 event probes, each of which was preceded by a specific orientation cue. These orientation cues provided participants with specific instructions for how to probe that followed each one. Specifically, participants were instructed on a trial-by-trial basis to either remember a specific event that occurred in their own past ("REMEMBER"), imagine a specific event that might occur in their own personal futures ("FUTURE"), or imagine President Obama participating in a specific event ("OBAMA"). President Obama was chosen as someone who is easily to imagine in a variety of situations, and is

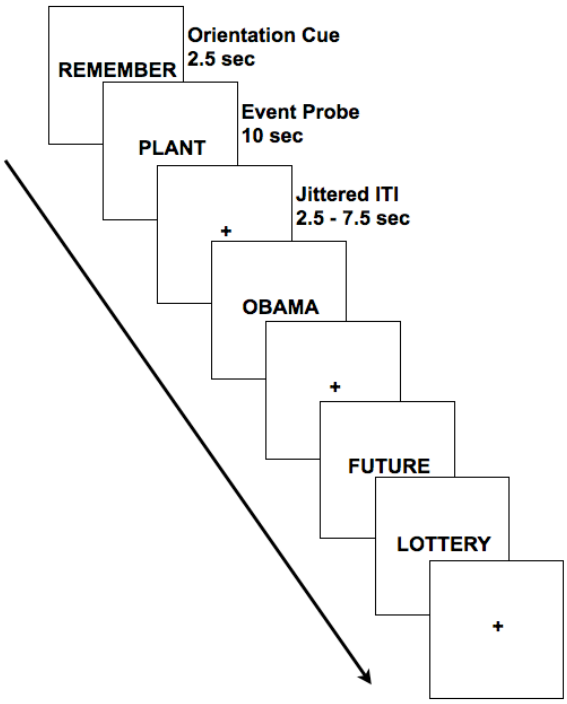

Figure 2. Summary of current study design. On a trialwise basis, participants are first provided with an orientation cue, describing the task they are about to perform. One frame later, they are given an event probe to help them simulate an event. On 20% of the trials, participants are provided only with the orientation cue. Plus signs represent 2.5-7.5 seconds of fixation between trials.

consistent with previous studies which have used political figures in such a manner (e.g., former U.S. presidents Bill Clinton [7] George Bush [20]; current German Chancellor Angela Merkel [21]). Participants saw each orientation cue for 2.5 seconds (1 TR) and during this time they were instructed to turn their attention toward thinking about the past, about the future, or about imagining President Obama, based on the cue with which they were just provided. Orientation cues were presented in the center of the screen, and participants were shown 30 of each type of cue.

Following this instruction on 80% of the experimental trials (72 total), participants were provided with an event probe: a short word or phrase that was meant to "help [them] form a given scenario mentally." This probe was presented for 10 seconds (4 TRs), and during this time participants were instructed to "remember or imagine, with as much vividness and detail as possible, an event related to the word or phrase" that was being presented. It was emphasized that the event probe was meant to be helpful, and that their envisioned scenario did not have to related directly to the probe itself. Participants were given the additional instruction that each event should be unique (i.e., they should not think about the same event for multiple event probes), and it should be specific in time and place. For events in the OBAMA condition, participants were explicitly told that they should perform the task without consideration to the temporal context of the event (i.e., whether it had occurred or had yet to occur). The event probe was presented in the center of the screen, and no delay was introduced between orientation cue and event probe presentations.

At the end of the 10-second period in which participants were simulating each event, the event probe was replaced by a fixation cross that appeared in the center of the

screen for 2.5-7.5 seconds. Participants were instructed that upon seeing the crosshair, they should stop thinking about a given event, clear their mind, relax, and await presentation of the next orientation cue.

The remaining 20% of the experimental trials (18 total) consisted of catch trials [19]. In these trials, participants saw the orientation cues that typically preceded each event, but no event probe. Instead, a fixation crosshair followed the orientation cue, just as it would typically follow the event probe. Because the event-probes occurred at a fixed interval following the orientation cue during normal ("compound") trials, these catch trials were used to separate the blood oxygen level dependent (BOLD) response associated with orientation cue presentation from that associated with event probe presentation (i.e., task-orientation signals from event simulation *per se,* for each condition). The ratio of 20% catch trials to 80% compound trials represents a compromise which allows enough catch trials to enable proper modeling of the orientation cue, while at the same time making the catch trials infrequent enough that they are not anticipated by participants, and is within the existing guidelines in the literature [18].

After completing this task, participants spent approximately 20 more minutes in the fMRI scanner performing an unrelated recognition memory task that will not be discussed in this report. In addition, approximately 8 minutes of resting-state data was collected prior to beginning the simulation task, and these data are likewise not discussed in this report.

Post-scan questionnaire

After exiting the scanner, participants completed a post-scan questionnaire, which

served as both a behavioral measurement of their phenomenological experiences, as well as a manipulation check. Subjects were re-presented with all of the event probes and the orientation cues associated with each probe, and were asked to make Likert-type ratings (1-4 scale) for each on several phenomenological characteristics. Specifically, subjects were asked to give a rating for vividness (4 = "most vivid), familiarity of scene in which the simulation was set (4 = "most familiar"), and difficulty in forming the scenario mentally (4 = "most difficult"). Previous studies using similar paradigms (e.g. [13]) have shown that subjects can reliably report such ratings after leaving the scanner. Subjects were also instructed to indicate, for each event, whether or not they were able to form a scenario mentally. We used this information for our manipulation check (see next section). Finally subjects were asked to provide detailed descriptions of three randomly selected events of each type (REMEMBER, FUTURE, OBAMA).

Manipulation check

Subjects who were unable to form scenarios for over 10% of the event probes were excluded from analysis. In addition, if the detailed descriptions provided by participants indicated that they did not follow task-instructions (e.g., if they did not constrain their scenarios to specific times and places), the participants were also excluded from analysis. As noted in the Participants section, two subjects were excluded was excluded for failing to meet these performance criteria, and one was excluded for failing to follow task-instructions.

fMRI data acquisition

Subjects were provided with foam pads and fitted with a thermoplastic mask fastened to the head coil to help stabilize head position (note: for 3 subjects, no masks

were available. For these subjects, they were held in place with foam and medical tape. None of these subjects displayed abnormal amounts of movement as compared with other participants in the study). All images were obtained with a Siemens MAGNETOM Tim Trio 3.0T Scanner (Erlangen, Germany) using a Siemens 12-channel Matrix Head Coil. A T1-weighted sagittal MPRAGE structural image was obtained for each participant (TE = 3.08ms, TR(partition) = 2.4s, TI = 1000ms, flip angle = 8 degrees, 176 slices with 1 x 1 x 1mm voxels) [22]. A T2-weighted turbo spin echo structural image (TE = 84ms, TR = 6.8s, 32 slices with 2 x 1 x 4mm voxels) in the same anatomical plane as the BOLD images was also obtained to improve alignment to an atlas. Gradient field maps were collected to estimate inhomogeneities in the magnetic field for each subject. An auto align pulse sequence protocol provided in the Siemens software was used to align the acquisition slices of the functional scans parallel to the anterior commissure-posterior commissure (AC-PC) plane and centered on the brain. Slices collected in this plane are parallel to the slices in the Talairach atlas [23], which is used for subsequent data analysis. Functional imaging was performed using a BOLD contrast sensitive gradient echo echo-planar sequence (TE = 27ms, flip angle = 90°, in-plane resolution= 4 x 4mm). Whole brain EPI volumes (MR frames) of 32 contiguous, 4mm-thick axial slices were obtained every 2.5 seconds. The first four functional image acquisitions of each run were discarded to allow for scanner equilibration.

Headphones dampened scanner noise and enabled communication with participants. An Apple iMac computer (Apple, Cupertino, CA) and PsyScope software [24] were used for display of visual stimuli. An LCD projector (Sharp model PG-C20XU) was used to project stimuli onto a MRI-compatible rear-projection screen (CinePlex) at the head of

the bore, which the participants viewed through a mirror attached to the coil (field of view = 21.5 degrees).

Preprocessing

Imaging data from each subject were pre-processed to remove noise and artifacts, including: i) correction for movement within and across runs using a rigid-body rotation and translation algorithm [25], ii) whole brain normalization to a common mode of 1000 to allow for comparisons across subjects [26], iii) temporal re-alignment using sinc interpolation of all slices to the temporal midpoint of the first slice, accounting for differences in slice time acquisition, and iv) gradient field map correction to correct for spatial distortions due to local field inhomogeneities using FSL's FUGUE (http://fsl.fMRIb.ox.ac.uk). Functional data were then resampled into 3mm isotropic voxels and transformed into stereotaxic atlas space [23]. Atlas registration involved aligning each subject's T1-weighted image to a custom atlas-transformed [27] target T1-weighted template (711-2B) using a series of affine transforms [28].

fMRI analysis based on the GLM

Data were modeled using a general linear model (GLM) approach [29]. Briefly, the model treats the data at each time point in each voxel as the sum of all effects present at that time point. Effects can be produced by events in the model and by error. Estimates of the time course of effects were derived from the model for each response category by coding time points as a set of delta functions immediately following onset of the coded event [18; 19]. The catch trials implemented in the design allow the orientation cue and event probe components of each compound trial to be coded separately in our model [18; 19]. The number of time points modeled in the GLM was 11 for cues and 10 for event

probes (27.5 or 25 seconds; event probe onset was 2.5 after cue onset in compound trials). For supplemental analyses comparing catch trials and compound trials, each condition was modeled with 11 time points; catch trials included "cue only" events, and compound trials both the cue set and event probe set were coded into the design matrix as a single event. Temporal jitter introduced between trials, combined with the catch trials, provided a sufficient number of independent equations to separately model the BOLD response for both the orientation cue and event probe time courses, and the ratio of 80% compound to 20% catch trials is within the guidelines suggested by prior literature [18; 19].

The three runs from each participant consisted of 185 frames (189 before discarding the first 4 frames of each run), and were concatenated into a single time series of 555 frames (370 in the case of the single subject who only contributed 2 functional runs). The GLM was coded with 6 separate regressors for different trial types (an orientation cue and event probe component for REMEMBER, FUTURE, and OBAMA conditions). Notably, separate regressors were not included for catch trial orientation cues and for compound trial orientation cues. That is, both catch trial cues and compound trial cues for the REMEMBER condition were treated as a single trial type, as were both types of cue for FUTURE and OBAMA conditions. Cues were combined in this way because participants had no way of determining one cue type from another before a trial ended, and because separate analysis of cue types produced nearly identical time courses (for related discussion, see Wheeler et al. [30]). In addition, each run included a trend term to account for linear changes in signal, and a constant term modeled the baseline signal. Time courses of the hemodynamic response for each condition were modeled using 10 or 11 time points, as described above.

Image processing was performed using in-house software (FIDL) written in IDL (Research Systems, Inc.). Each participant's data were resampled into 3 x 3 x 3mm stereotaxic atlas space [23] during processing. All Talairach atlas coordinates were converted to MNI152 space using in-house software written by Avi Snyder. Statistical maps were projected onto a partially inflated surface representation of the human brain using CARET software [31], and were projected onto volumes using MRICron [32].

Voxelwise t-tests

Main experimental questions concerned what regions showed changes in activity related to orientation cues, and what differences existed during event simulation periods when either remembering past events or imagining future events. For orientation-cue analysis, we conducted voxelwise *t*-tests, comparing aggregated activity across all orientation cue types to baseline. Activity was binned by time points, averaging activity across 2 time points at a time as implemented by FIDL. In addition, we conducted voxel-wise *t*-tests between the REMEMBER and FUTURE event probes, aggregating activity across the 4th and 5th time points following event probe onset. These time points were chosen based on prior studies showing that regions involved in episodic simulation tend to peak fairly late (e.g., [7; 9]), and we wished to capture activity levels around the peak of the BOLD response.

The uncorrected contrast image was smoothed using a 6mm sphere kernel. The obtained *t*-test image was Monte Carlo corrected at a z-score of 3 with at least 17 contiguous voxels, providing a corrected $p < .05$ [33]. Regions located in white matter or ventricles were removed from the analysis.

Analysis of time courses

After defining regions from the voxelwise *t*-test, BOLD activity during the 4th and 5th time points for the 3 event probe conditions (REMEMBER, FUTURE, and OBAMA) within each region were compared using *t*-tests. While by definition the REMEMBER and FUTURE conditions were significantly different in these regions, we were also interested in how activity levels differed between these two conditions and the OBAMA condition.

Voxelwise analysis of compound trials for replication of previous work

A voxelwise condition x time repeated measures ANOVA, with 3 levels of condition (REMEMBER, FUTURE, and OBAMA) and 11 levels of time (11 time points) was conducted to compare activity for "compound" trials. This technique allowed for an appropriate comparison with previous studies using a similar paradigm to explore episodic simulation [7].

The uncorrected interaction (condition x time) image for compound trials was smoothed using a 6mm sphere kernel. An automated peak-finding algorithm written by Avi Snyder searched for the location of peaks exceeding a *z*-score of 3. Peaks under 10mm apart were consolidated by averaging coordinates. A 10mm (19 voxel) sphere centered on the peak coordinate was used to extract time courses.

RESULTS

Behavioral results were consistent with previous studies

Behavioral results were broadly consistent with previous studies (for review and discussion, see [13] and are summarized in Table 1. Participants rated events in the REMEMBER condition as being more generally more vivid, as occurring in more familiar locations, and as being easier generate than events in either the FUTURE or

OBAMA conditions. FUTURE events were likewise more vivid, occurred in more familiar locations, and were easier to generate than events in the OBAMA condition. Despite these differences in perceived vividness, scene familiarity, and difficulty, the number of events that participants failed to generate did not differ between conditions. Unless noted otherwise, behavioral effects were considered significant at $p < .05$, two-tailed. Effect sizes were calculated using G*Power3 [34].

Vividness

A one-way ANOVA revealed a significant effect of condition for vividness ($F(2,71) = 33.17$, $p < .05$). Subsequent pairwise testing revealed that subjects rated events from the REMEMBER condition as more vivid than those of the FUTURE condition ($t(46) = 5.24$, $p < .001$, $d = 1.52$) or events in the OBAMA condition ($t(46) = 8.66$, $p < .001$, $d = 2.52$). Events in the FUTURE condition were also significantly more vivid than those events in the OBAMA condition ($t(46) = 2.85$, $p < .01$, $d = 0.83$).

Scene Familiarity

A similar pattern was obtained for reports of scene familiarity. A one-way ANOVA revealed a significant effect of condition ($F(2,71) = 26.59$, $p < .001$). Subsequent pairwise testing revealed that subjects rated the settings of events from the REMEMBER condition as more familiar than those of the FUTURE condition ($t(46) = 3.88$, $p < .001$, $d = 1.11$) and OBAMA condition ($t(46) = 11.31$, $p < .001$, $d = 3.25$). Event locations in the FUTURE condition were significantly more familiar than those events in the OBAMA condition ($t(46) = 5.70$, $p < .001$, $d = 1.63$).

Difficulty

Difficulty in forming a scenario mentally followed the same pattern as was

Table 1. Mean characteristics of event types

	REMEMBER		FUTURE		OBAMA	
	Mean	SEM	Mean	SEM	Mean	SEM
Vividness	3.44	0.05	2.91	0.09	2.56	0.09
Familiarity	3.41	0.06	2.91	0.12	1.46	0.05
Difficulty forming	1.46	0.05	1.87	0.10	2.31	0.09
No-event instances	0.63	0.18	0.75	0.24	0.75	0.26

SEM = standard error of the mean

observed for vividness and scene familiarity. The one-way ANOVA was significant ($F(2,71) = 53.1$, $p < .001$), and pairwise testing revealed that simulating events in the REMEMBER condition was less difficult than events for the FUTURE condition ($t(46) = -3.68$, $p < .001$, $d = 1.07$) or OBAMA condition ($t(46) = -8.24$, $p < .001$, $d = 2.38$), and events in the FUTURE condition were significantly easier to form than those events in the OBAMA condition ($t(46) = -3.30$, $p < .01$, $d = 0.96$).

Event generation failures

While events in different conditions were, on average, rated differently in their phenomenological characteristics, they did not differ in how frequently subjects reported being unable to generate events for different conditions; the ANOVA did not reveal any significant differences ($F(2,71) < 1$)**.**

Whole brain t-tests reveal regions showing activations and deactivations related to orientation cue presentation.

Areas of activation related to orientation cue onset (*t*-tested against zero) are showin in Figure 3. Regions showing early responses to orientation cues show task-induced activations and fall within visual cortex and the fronto-parietal control network [35]. Later responses also include task-induced deactivations, and these fall within areas commonly considered to be a part of the default network [36-38].

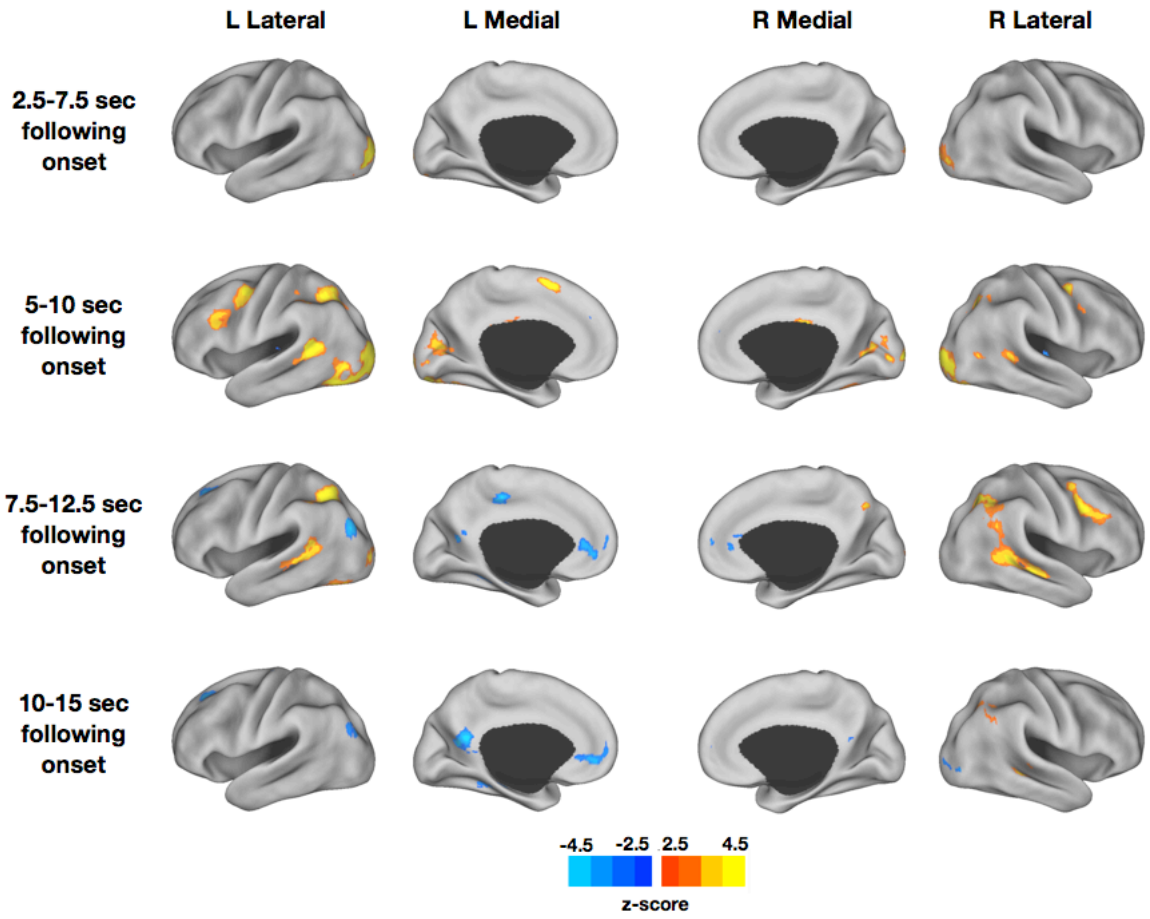

Figure 3. Statistical maps of cue-related activity across all cue types during several time windows. Cue-induced activations tend to occur rapidly following cue-onset, while deactivations occur several time points later. Each bin represents activity aggregated across 2 MR frames, as estimated using an FIR model. *t* values were converted to z-scores and projected onto a cortical surface using CARET software [31].

Whole-brain t-tests reveal 3 regions that show differences between REMEMBER and FUTURE event simulation

The primary comparison of interest is the voxelwise t-test of REMEMBER and FUTURE event probes. These results are shown in Fig. 4a. Three ROIs emerge after Monte Carlo correction, demonstrating significantly more activity for REMEMBER than FUTURE event probe periods. These ROIs were located in bilateral posterior parahippocampal cortex (PHC) and in the right retrosplenial cortex (Rsp). No regions were located demonstrating significantly greater activity for FUTURE than for REMEMBER conditions.

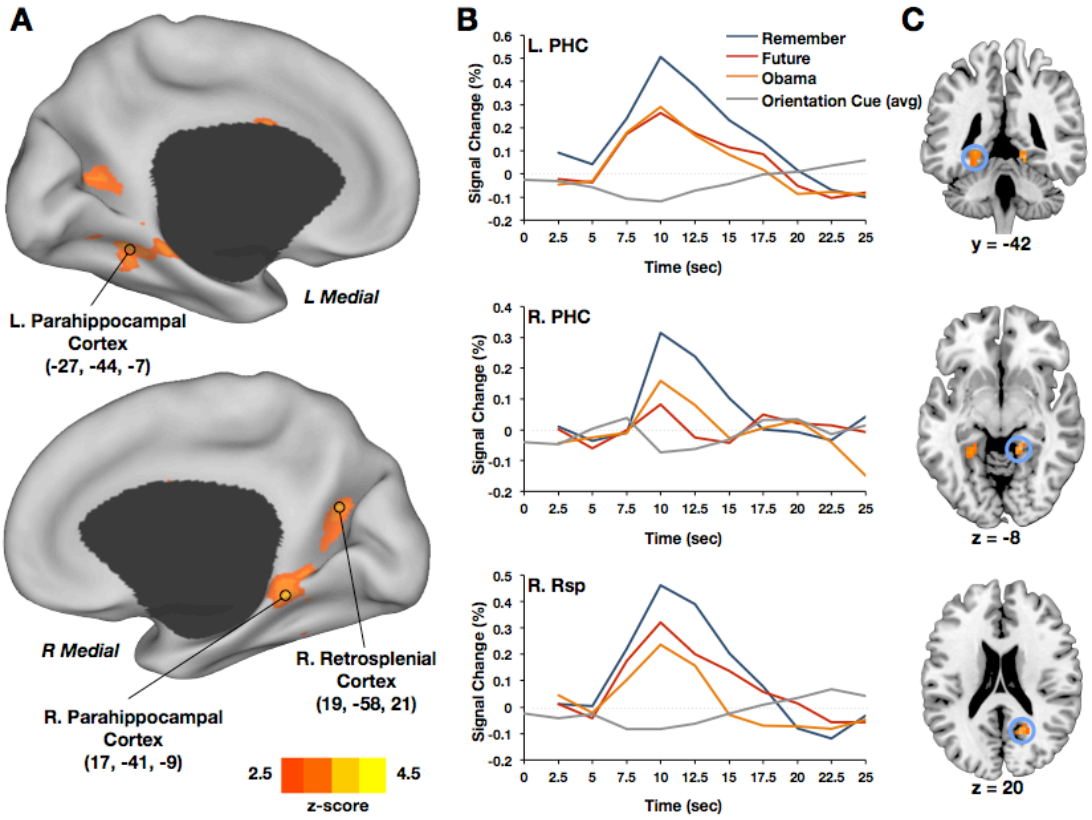

Figure 4. Regions identified in voxelwise *t*-test showing differential activity for REMEMBER and FUTURE conditions. A) Voxel clusters surviving Monte Carlo correction consist of regions in bilateral parahippocampal cortex and right retrosplenial cortex, projected onto a partially inflated CARET brain surface [31]. B) Time courses extracted from these regions show preferential activation for events in the REMEMBER condition. In addition, these regions show slight deactivation in response to the orientation cue. C) A volumetric view of the activations in each region, using MRIcron [32].

Time course analysis of regions showing preferential activity for remembering

Time courses were extracted for the three ROIs identified in the *t*-test analysis. Pairwise comparisons were then made between each condition in each ROI. While by definition the activity is significantly different between REMEMBER and FUTURE conditions in these ROIs (as that is how they were defined), it is notable that activity for REMEMBER probes is greater than for OBAMA probes in all 3 regions (see Fig. 4b; Table 2). Furthermore, no significant differences emerged between the FUTURE and OBAMA conditions in any of the three ROIs.

Time course analysis reveals deactivation, relative to baseline, for the orientation cue component of trials (Figs 3; 4b) in both the left PHC ($t(23) = -2.92$, $p < .01$, $d = 1.20$)

Table 2. Difference scores between conditions in ROIs identified in voxelwise *t*-test.

Remember *vs.* Future

Region	*t*-score	*z*-score	*p*-value (<)
L PHC	4.64	3.75	0.001
R PHC	3.86	3.35	0.001
R Rsp	4.50	3.77	0.001

Future *vs.* Obama

Region	*t*-score	*z*-score	*p*-value (<)
L PHC	-0.17	-0.17	*n.s.*
R PHC	-1.68	-1.61	*n.s.*
R Rsp	1.17	1.17	*n.s.*

Remember *vs.* Obama

Region	*t*-score	*z*-score	*p*-value (<)
L PHC	3.43	3.06	0.01
R PHC	2.60	2.41	0.05
R Rsp	4.30	3.65	*n.s.*

PHC = Parahippocampal Cortex; Rsp = Retrosplenial Cortex. Region coordinates (x, y, z): L PHC (-27, -44, -7); R PHC (17, -41, -9); R Rsp (19, -58, 21).

and right Rsp ($t(23) = -2.79$, $p < .05$, $d = 1.16$) regions, and no significant deviation from baseline activity in the right PHC region ($t(23) = -1.56$, $p = .13$). Furthermore, for reach region, activity related to the orientation cue was significant different than activity related to the event probe (left PHC ($t(23) = -5.08$, $p < .001$, $d = 2.12$); right PHC = ($t(23) = -2.37$, $p < .05$, $d = 0.99$); right Rsp ($t(23) = -6.15$, $p < .001$, $d = 2.57$)). In other words, for two of the three regions identified in the previous *t*-test, the time course of the BOLD activity associated with the orientation cue was negative, even though the activity related to the event probe component of the trial was positive, and for all regions, cue-related responses were significantly different than responses to event probes. Cue-related activity is shown as an average across all conditions because a condition x time ANOVA did not reveal any significant effects in any of the three regions.

An analysis of variance for the compound trials replicates previous results

Results from the voxelwise condition x time ANOVA for compound trials are shown in Fig. 5. Broadly speaking, the statistical map obtained in the current study (Fig. 5b) overlaps with the map obtained by Szpunar et al. ([7]; Fig. 5a), indicating that participants were not substantially changing the manner in which they approached the

experimental task, despite deviations from previous methods.

Examination of separated cue and probe time courses in other regions identified by Szpunar et al. [7]

The finding that orientation cue and event probe time courses were of opposite directions in several ROIs prompted us to examine other regions identified by Szpunar et al. as being involved in episodic simulation [7] that also came out of our compound trial ANOVA. We selected a region in left superior frontal gyrus and a region in ventromedial prefrontal cortex (Fig. 6a). We compared the time courses extracted using compound trial and separated cue and event probe analyses. Orientation cues was were associated with deactivations relative to baseline for both the superior frontal ($t(23) = -4.22$, $p < .001$, $d = 1.76$) and ventromedial prefrontal ($t(23) = -3.14$, $p < .01$, $d = 1.30$) regions (Figs. 6b, 6c). Consequently, by separately modeling the cue, the event probe activity increased in each region for each condition. As with the bilateral PHC and right Rsp region, no differences were found between different orientation cue conditions; the condition x time ANOVAs were not significant.

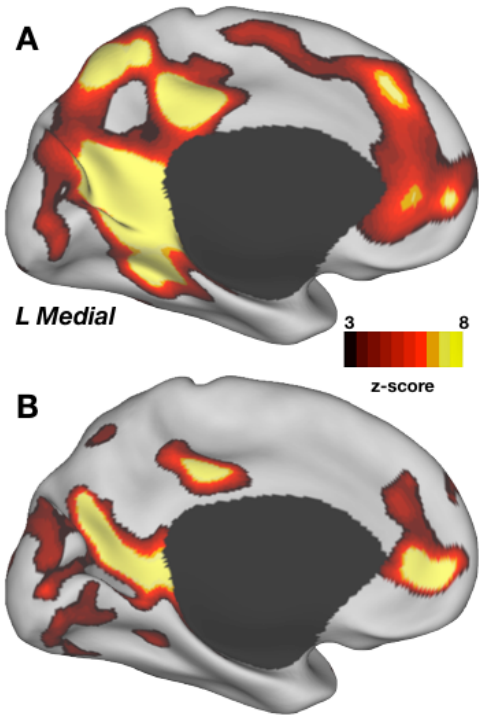

Figure 5. Statistical maps based on compound trial analysis replicate those reported previously. A) The voxelwise condition x time ANOVA map reported by Szpunar et al. [7], from a task in which participants were asked to remember events from their own past, imagine events from their own futures, or imagine Bill Clinton participating in events. B) A voxelwise condition x time ANOVA map from the present study, using compound trials, in which participants remembered events from their own past, imagined events from their own futures, or imagined Barack Obama participating in events.

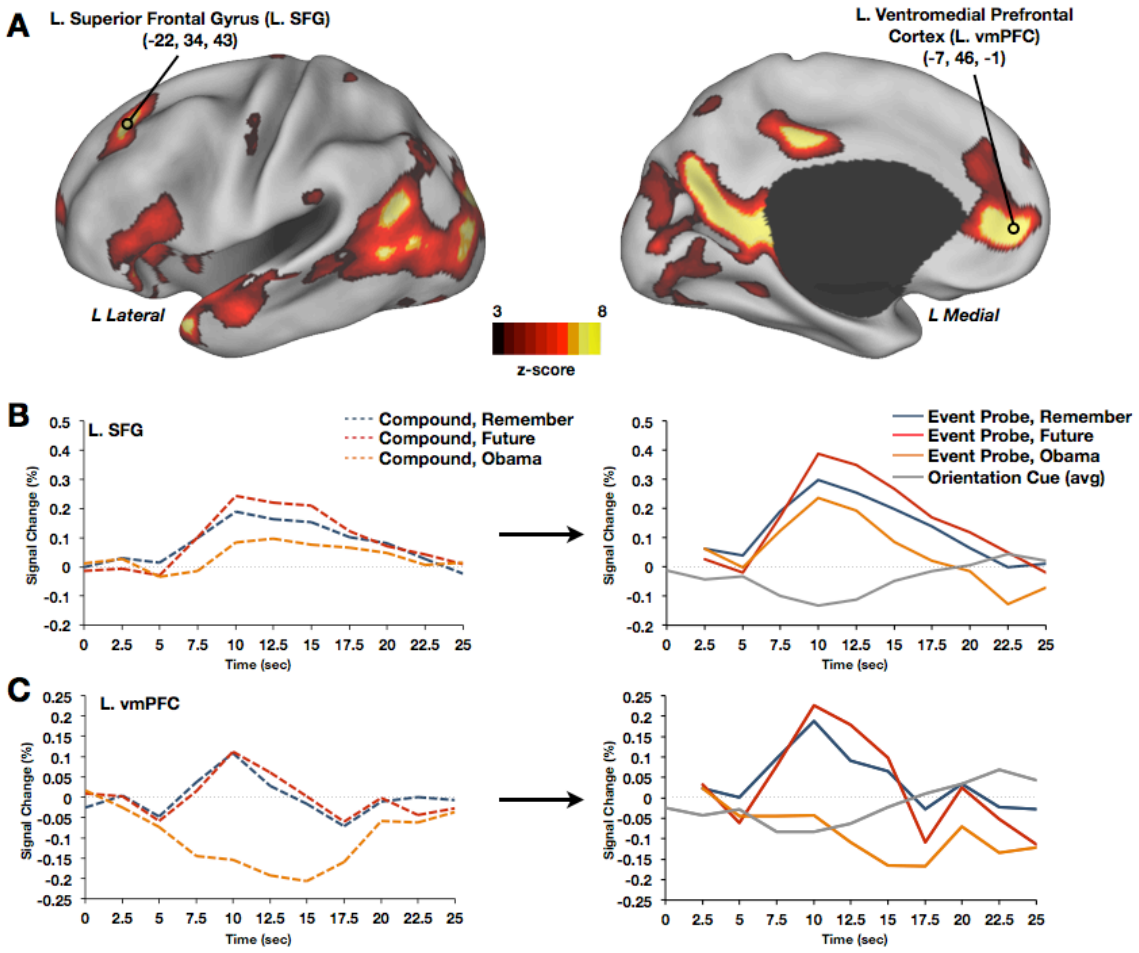

Figure 6. Regions outside of those obtained in the *t*-test analysis show time courses of opposite directions during episodic simulation tasks. A) Sample regions were selected from left superior frontal gyrus and ventromedial prefrontal cortex. B & C) By separating orientation cue-related activity from event probe-related activity, one can observe time courses going in opposing directions around baseline, suggesting multiple, temporally overlapping processes. Offloading the orientation cue therefore provides a more pure observation of the signal related to event probe simulation. SFG = superior frontal gyrus; vmPFC = ventromedial prefrontal cortex.

DISCUSSION

Summary

This study replicates and extends previous work focusing on the neural correlates of episodic simulation. Specifically, this current report demonstrates separable components within a typical simulation trial: BOLD activity in response to a presented orientation cue was separated from BOLD activity in response to the act of simulation itself. This novel approach revealed that the time courses associated with these components were of

opposing directions across a number of regions previously implicated in episodic simulation. By effectively offloading the cue component, we found that regions involved in simulation might show BOLD responses were of greater magnitude than has previously been assumed (Fig. 6). In addition, we found for the first time in an episodic simulation paradigm regions that showed more activity when recalling past events than imagining future events (Fig. 4).

Replicated previous work

An important check when in attempting to apply a catch trial design to episodic simulations was the change in how participants were shown stimuli. Whereas in all previous studies orientation cues and event probes were shown simultaneously, in this experiment we temporally separated the two components such that participants saw the orientation cue prior to being shown the event probe. In order to ensure that this difference in presentation did not significantly alter how participants engaged in the task, we based our catch trial design on a well-characterized paradigm used by Szpunar et al. [7]. When modeling compound trials together and conducting an ANOVA to compare activity across REMEMBER, FUTURE, and OBAMA conditions, we found highly similar statistical maps (Fig. 5). This basic check does not guarantee that participants behaved identically in this study to the earlier Szpunar et al. study (i.e., some differences may still be induced by showing orientation cues and event probes separately), but it does suggest that any differences we observed when separating cue and event probe activity were true differences, and not an artifact of differences in how stimuli were presented.

Differences in orientation cue and event probe time courses

A comparison of the time courses of orientation cue- and event probe-related

activity ROIs implicated in episodic simulation demonstrates that whereas the BOLD signal related to event simulation itself is positive, orientation-related signals are typically slightly negative (i.e., orientation is associated with deactivation in regions engaged during episodic simulation). This negative response was fairly sluggish, peaking relatively late in each trial (about 12.5 seconds after cue onset; the same TR in which the event probe activity also typically peaked). The relatively small, slow response to orientation cues effectively reduced the observed BOLD response to all types of simulation trials. No significant differences in orientation cue activity were found in this report. Given the relatively small number of catch trials incorporated in the design, it is possible that these null effects are a result of a lack of sufficient power relating to the orientation cue signal, especially given the pattern of numerical differences observed in ROIs identified in the REMEMBER > FUTURE contrast (Fig. 4). While our proportions of compound trials to catch trials was consistent with that suggested by the literature [18], it is reasonable to suspect that the absolute number of trials was too small to allow us to directly compare activity across cue conditions. Future work will be necessary to examine this cue component of simulation trials to better understand different regional BOLD responses sensitive to different "modes" or task sets, which appears to be a critical next step in understanding processing differences between types of mental simulation task.

Cue-related activity can distort the BOLD signal related to event simulation

Despite the lack of power to statistically test for differences between orientation-related BOLD activity, the fact that it was consistently negative is informative from a theoretical standpoint. Regions commonly engaged by episodic simulation tasks, such as

medial prefrontal cortex, posterior cingulate cortex, and retrosplenial cortex, fall within what is known as the default network ([36; 37], see also [38]). Regions within the default network were initially identified as being consistently less active during a variety of task conditions than during periods of awake rest [36; 39]. More recent characterizations tend to suggest that default regions can be activated above baseline levels when one's attention is directed internally (as in a memory retrieval task) rather than externally (as during a variety of visuospatial tasks) (for recent discussion, see [40; 41]).

Deactivations observed in this study during orientation cue periods occur in a variety of default regions, and may suggest that while one is preparing to think about either the past or the future (e.g., when one is entering a retrieval mode), default regions are nevertheless sensitive to the orientation to the words on the screen. That is, despite attention being turned inward in preparation to perform a memory task, the dominant BOLD response during orientation across a number of default regions is a slight deactivation. This should highlight the importance of separating orientation signals from other task-related signals, not only in our own paradigm but in memory studies more broadly.

In addition, while orientation cue conditions did not significantly differ from one another in this study, it should be stressed that they were not numerically equivalent. As such, removing them did not simply remove a constant and globally inflate all event probe activity time courses to an equal degree. These slight differences in orientation-related activity may differentially affect each event probe condition, which may explain why in previous studies the ROIs identified in PHC and Rsp were not observed.

A small network of regions in posteromedial cortex and the medial temporal lobe supports "true remembering" in episodic simulation

In this study, only bilateral PHC and right Rsp regions emerged as showing greater activity for REMEMBER than FUTURE event probes. PHC and Rsp have been identified as a functionally-coupled unit using both functional and resting-state fMRI techniques (for recent review, see [42]; for resting-state descriptions see [43; 44]). fMRI studies that have shown coactivation of these regions tend to involve some form of contextual processing. PHC and Rsp tend to activate more in episodic memory studies when one can recollect specific contextual details, as in successful retrieval of source memory information (e.g., [45]). Evidence from the neuropsychology literature suggests that patients suffering damage to Rsp show retrograde amnesia, with symptoms similar to those in hippocampal patients [46], and it appears as though both Rsp and the hippocampus are highly interconnected anatomically [47; 48]. This literature lends converging support to the characterization of Rsp as being involved in episodic memory retrieval.

Beyond the realm of episodic memory, PHC and Rsp have been linked to spatial processing, spatial memory, and navigation. One hypothesis is that these two regions represent complementary information within these domains, with the PHC representing visuospatial information (e.g., the "layout" of a scene; [49]), and the Rsp providing a means of utilizing this information to orient oneself in space [50]. It has also been demonstrated in a parallel line of research that objects that are typically restricted to specific spatial contexts tend to activate both PHC and Rsp more strongly than objects that may occur across a variety of contexts (e.g., [51; 52]). It seems therefore that these

regions enable one to mentally navigate 3-dimensional spaces, either when provided with example scenes or when generating them internally (for further discussion, see [42]).

PHC and Rsp activity has previously been implicated in episodic simulation

In addition to the above, both PHC and Rsp have been implicated in retrieving autobiographical memories (e.g., [53; 54]) and in episodic simulation tasks (e.g., [7; 9]). An important observation from a study by Szpunar et al. [9] demonstrated greater PHC and Rsp activity for imagining oneself in familiar rather than unfamiliar contexts. Combined with the above characterization of PHC and Rsp as a functional module involved in spatial and contextual processing, it seems reasonable to assert that PHC and Rsp are acting during simulation to construct an episode within a particular contextual environment, a sentiment recently echoed in a review by Ranganath and Ritchey [42].

Given this putative functional role, our findings of greater activity for remembered event periods than imagined future periods begins to make sense. Remembered events will necessarily have more recollective detail than will imagined future events, or imagined events involving President Obama. To the extent that these details will provide a richer "mental landscape" for events, more activity should be elicited selectively for the Remember conditions.

This conclusion is partially supported by subjective ratings. Remembered events tended to be more vivid and occur in more familiar locations than did imagined events, either of one's future or involving President Obama. However, subjective reports also suggested that imagined future events were more detailed and occurred in more familiar locations than did imagined events involving President Obama, and no such difference was observed in the BOLD response in any of our ROIs (in fact, in R PHC, the opposite

pattern was observed numerically). This may be due to the manner in which the subjective reports were collected, as retrospective ratings after subjects left the scanner. Although previous work has demonstrated them to be reliable [7], they may not contain enough fine-grained information to accurately reflect activity in any of our obtained regions. A supplemental set of analyses regressed out each phenomenological measure from the obtained BOLD signal, and results were indistinguishable pre- and post-regression for any factor. Given that other reports have shown relationships between subjective reports of "reliving" and activity in Rsp [55], it remains for future work to clarify the relationship between subjective experiences and BOLD activity in our ROIs.

_t_-tests revealed no areas in which FUTURE conditions show greater activity than REMEMBER conditions

Another notable feature of our results is the lack of regions showing greater activity for events in the FUTURE than in the REMEMBER conditions. Although numerically FUTURE conditions elicited more activity in some regions previously identified as showing greater activity for imagined than remembered events (e.g, a region in left SFG; see Fig. 6; [7; 9; 53]), no statistically reliable differences were found anywhere in the brain. There are several possible reasons for failing to obtain results commonly found in the extant literature.

One possibility, discussed above, is that activity related to the orientation cue is slightly different between REMEMBER and FUTURE conditions, such that many regions deactivate slightly more in response to the REMEMBER cue than FUTURE cue. If the cue were not offloaded from the event probe, then it would appear as though greater activity was elicited for compound FUTURE trials than compound REMEMBER

trials. This observed difference would be in line with previous observations, but would imply that the simulation processes are not different between remembered and imagined events of oneself in time. Instead, differences in the mental set adopted to perform these operations would be what caused them to appear as differ in previous experiments. This possibility is intriguing, but results from the current study cannot speak to significant differences between orientation cue conditions. Future research, focused on examining this orientation component, will be necessary to assess the utility of this explanation.

A second possibility is that sampling variability within our study was greater than in some previous studies. This is a fairly uninteresting possibility, but it may be the case, and future replication of the present results will speak further to this possibility's utility.

A final possibility is that the subtle differences between our study and previous methods is responsible for the lack of regions demonstrating greater activity for REMEMBER and FUTURE conditions (Fig. 4). Despite our attempt to ensure that participants were not changing how they approached this task as compared to previous tasks (Table 1; Fig. 5), it may be the case that separating orientation cue and event probe instructions across two frames changed certain task parameters. For instance, as compared to [7], separating instructions as we did may have changed the amount of time spent generating an event as compared to simulating it. Since no reaction times were collected, no answer to this possibility exists in the current experiment. To the extent that including catch trials did change participant behavior in some way, future studies employing a design similar to that used here will clarify what these differences may be, and how they affected the present results.

Final conclusions

In sum, the data presented here present an intriguing possibility about the relationship between BOLD activity related to adopting specific mental sets when engaging in different mental simulation tasks, and the activity related to actually carrying out the mental simulations. By "offloading" the orientation cue component of the signal, we observed novel differences that have never before been observed as participants simulated different types of events, showing greater activity for remembered than for imagined events, and these differences could not be explained simply by subjective experience ratings. Future work will have to clarify the role of the orientation-cue as one approaches these different simulation tasks.

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