RAPID COMMUNICATION

WILEY

Increased hippocampus to ventromedial prefrontal connectivity during the construction of episodic future events

Karen L. Campbell[1] 🆔 | **Kevin P. Madore[2]** | **Roland G. Benoit[3]** |
Preston P. Thakral[4] 🆔 | **Daniel L. Schacter[4]** 🆔

[1]Department of Psychology, Brock University, St Catharines, Ontario, Canada

[2]Department of Psychology, Stanford University, Stanford, California

[3]Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

[4]Department of Psychology, Harvard University, Cambridge, Massachusetts

Correspondence
Karen L. Campbell, Department of Psychology, Brock University, 1812 Sir Isaac Brock Way, St. Catharines, ON L2S 3A1, Canada.
Email: Karen.Campbell@brocku.ca

Funding information
National Institute of Mental Health Grant, Grant/Award Number: MH060941 (to D. L. Schacter); and a Tier 2 Canada Research Chair to K. L. Campbell.

Abstract

Both the hippocampus and ventromedial prefrontal cortex (vmPFC) appear to be critical for episodic future simulation. Damage to either structure affects one's ability to remember the past and imagine the future, and both structures are commonly activated as part of a wider core network during future simulation. However, the precise role played by each of these structures and, indeed, the direction of information flow between them during episodic simulation, is still not well understood. In this study, we scanned participants using functional magnetic resonance imaging while they imagined future events in response to object cues. We then used dynamic causal modeling to examine effective connectivity between the left anterior hippocampus and vmPFC during the initial mental construction of the events. Our results show that while there is strong bidirectional intrinsic connectivity between these regions (i.e., irrespective of task conditions), only the hippocampus to vmPFC connection increases during the construction of episodic future events, suggesting that the hippocampus initiates event simulation in response to retrieval cues, driving activation in the vmPFC where episodic details may be further integrated.

KEYWORDS

dynamic causal modeling, functional magnetic resonance imaging, hippocampus, imagination, ventromedial prefrontal cortex

1 | INTRODUCTION

Mounting evidence indicates that imagining future experiences (episodic simulation) and remembering past experiences (episodic memory) rely on similar constructive processes that reinstate and recombine information (for a recent review, see Schacter, Benoit, & Szpunar, 2017). In line with this view, both past and future events activate the same core network of brain regions, including the medial temporal lobes (MTL) extending to posterior cingulate/retrosplenial cortex, ventromedial prefrontal cortex (vmPFC), dorsomedial prefrontal cortex, and lateral parietal and temporal areas (Benoit and Schacter, 2015). Although the unique contribution made by each of these regions to episodic simulation remains unclear, neuropsychological and neuroimaging studies have focused in particular on two regions: the hippocampus and vmPFC (for discussion, see Bertossi, Tesini, Cappelli, & Ciaramelli, 2015; Kurczek et al., 2015; Schacter, Addis, & Szpunar, 2017). Neuroimaging studies suggest that hippocampal activity tracks with the level of retrieval or recombinatorial demand (cf. Gaesser,

Spreng, McLelland, Addis, & Schacter, 2013; Thakral, Benoit, & Schacter, 2017). In contrast, vmPFC activity is stronger when the elements of a simulated event are more familiar (Benoit, Szpunar, & Schacter, 2014; Szpunar, Chan, & McDermott, 2009) or self-relevant (D'Argembeau et al., 2010). Thus, the vmPFC may play a critical role in incorporating one's sense of "self" into simulated events and integrating activated representations with existing knowledge structures or schemas (Benoit et al., 2014; Demblon, Bahri, & D'Argembeau, 2016; van Kesteren, Ruiter, Fernández, & Henson, 2012).

Importantly, the hippocampus and vmPFC do not function in isolation: They form part of the same "medial temporal lobe subsystem" within the larger default/core network (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Campbell, Grigg, Saverino, Churchill, & Grady, 2013), and dynamically interact to support memory and imagination functions (Brown et al., 2016; Ritchey, Libby, & Ranganath, 2015; Zeithamova, Dominick, & Preston, 2012). However, measures of functional connectivity, or the degree to which activity in different brain regions correlate over time, can only tell us part of the story. A
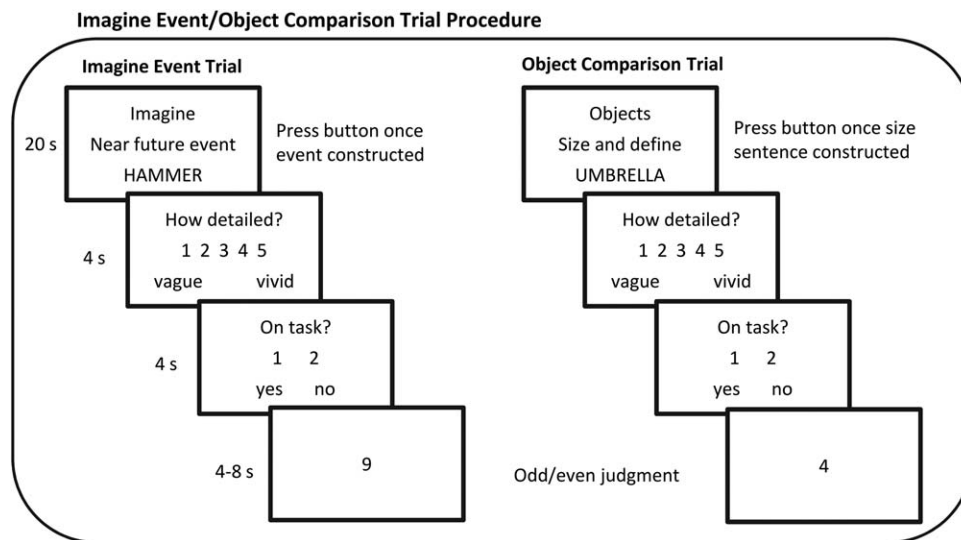
Imagine Event/Object Comparison Trial Procedure

FIGURE 1 Overview of experimental procedure. On *Imagine* trials, participants were instructed to silently generate a novel future event that related to the cue, that was detailed, plausible, specific to one place and time, and viewed from a field perspective. They pressed a button once the event was constructed and continued to elaborate for the remainder of the trial. On *Object* trials, participants were instructed to silently generate two objects that related to the object cue and put these objects into a size sentence (e.g., "Board is larger than hammer is larger than nail"). They pressed a button once the sentence was constructed and then continued to think of definitions for each object

more thorough understanding of how these regions interact to give rise to simulated events requires a measure of *effective connectivity*, or the causal influence of one region on another (Friston, 2011). Understanding the dynamics behind hippocampal-vmPFC interactions during episodic future thinking may help further elucidate the unique contribution made by each of these regions.

To this end, we scanned participants ($N = 32$, 20 females; mean age = 21.0 years, $SD = 2.38$) using functional magnetic resonance imaging (fMRI) while they imagined future events in response to object word cues or performed a nonepisodic control task (see Figure 1; data from Madore, Szpunar, Addis, & Schacter, 2016, see that paper for fMRI acquisition and prepocessing details). Peak regions (imagine > control; $p < .05$, FWE corrected) were identified in the vmPFC [$x = 0$, $y = 50$, $z = -14$] and left anterior hippocampus [$x = -24$, $y = -16$, $z = -18$] and subject-specific time series were extracted separately for each run (using a 6-mm radius sphere centered at individual maxima within 6 mm of the group peak, adjusted for effects of interest). We opted for the left anterior hippocampus because this region is consistently related to episodic simulation (e.g., Addis, Wong, & Schacter, 2007; Martin, Schacter, Corballis, & Addis, 2011) and more recently, has been shown to be modulated by a specificity induction known to increase episodic retrieval (Madore et al., 2016). Since our primary interest here was effective connectivity during event construction in general, rather than the effect of induction, we collapsed across the specificity and control inductions used by Madore et al. (2016) to provide 6 runs of task data per subject (thus maximizing our power).[1] Further, we focused on the construction phase, rather than the elaboration phase, because this portion of the trial places the highest demands on retrieval and recombination, as indicated by the finding that effects of the episodic specificity induction were observed only during construction (Madore et al., 2016).

Dynamic causal modeling (DCM) was used to examine effective connectivity between the vmPFC and hippocampal nodes during initial event construction. The advantage of DCM is that it not only provides a measure of ongoing (or endogenous) effective connectivity between regions, but also a measure of how these directed connections are modulated by task demands (Friston, Harrison, & Penny, 2003; Stephan et al., 2010). The user specifies a number of (anatomically feasible) neuronal models and these are tested against the observed data, yielding three sets of parameters: (a) *endogenous parameters* reflecting the strength of context-independent connectivity between regions (in this case, connectivity between the hippocampus and vmPFC throughout the run, irrespective of condition), (b) *modulatory parameters* reflecting context-dependent changes in connectivity between regions (in this case, connections altered on imagination trials), and (c) *extrinsic parameters* reflecting the influence of driving inputs on the system (in this case, all trial and rating phase onsets). Bayesian Model Selection (BMS) is used to determine which model, or family of models (sharing some common element), offers the best fit to the data (Penny et al., 2010). Given previous demonstrations of information flow from the hippocampus to vmPFC in other related paradigms (e.g., McCormick, St-Laurent, Ty, Valiante, & McAndrews, 2015; Place, Farovik, Brockmann, & Eichenbaum, 2016), as well as extensive work showing that the hippocampus acts as an index to episodic details stored elsewhere in the neocortex (for a recent review, see Moscovitch, Cabeza, Winocur, & Nadel, 2016), we hypothesized that the hippocampus would drive activation in the vmPFC during the construction of episodic future events.

Our model space consisted of four families of models, each differing in the modulatory effect of imagination (modeled as events of zero duration 2 s after cue onset on imagination trials; see Figure 2). All models had bidirectional intrinsic connections between the
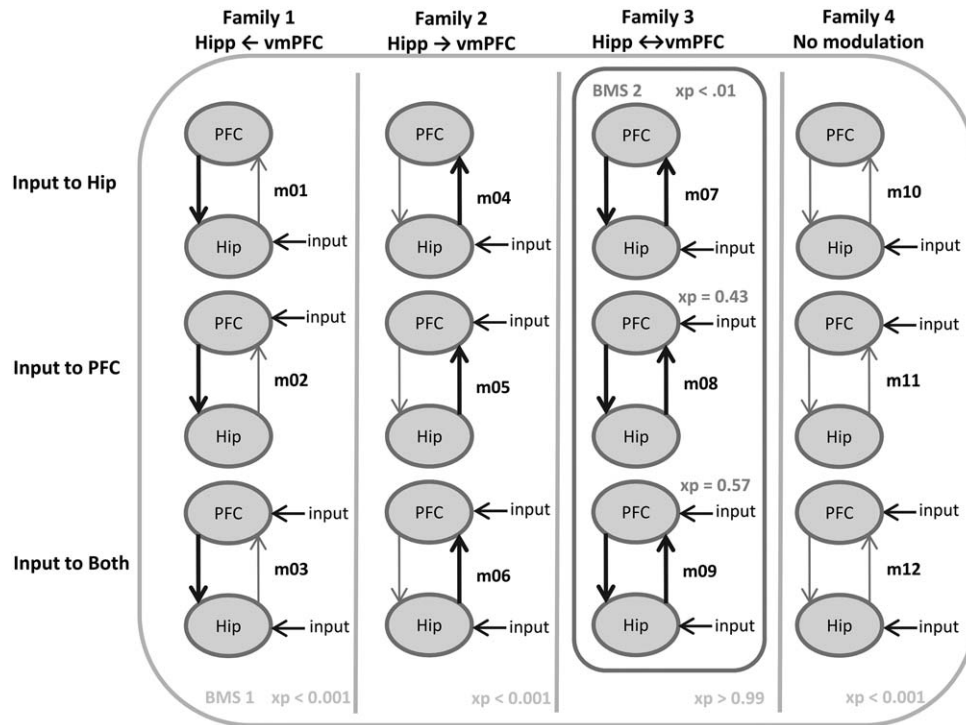
FIGURE 2 Model specification. Models are divided into 4 families, differing in the modulatory effect of imagination (shown along top and with bold arrows). Within each family, models differ based on where driving inputs enter the system (shown along left-hand side). Exceedance probabilities (xp) for BMS 1 (i.e., at the family level) are shown for each family at the bottom of the figure, whereas xp's for models within the winning family are shown in the column for Family 3

hippocampus and vmPFC, as well as within-region inhibitory autoconnections. Within each family, driving inputs (corresponding to all trial and rating phase onsets, modeled as events of zero duration) could enter through the hippocampus, vmPFC, or both regions. Models were estimated separately for each participant and each run, and the estimated models were then submitted to a random-effects BMS analysis at the family level to determine the winning family. The results showed that Family 3, with imagination affecting connectivity in both directions, offered the best fit to the data with an exceedance probability (xp; or the probability that one model/family is more likely than any other) greater than 0.99.

We next compared the models within Family 3 to identify a winning model. Model 8 (with driving inputs entering through the vmPFC alone) and model 9 (with driving inputs entering through both the vmPFC and hippocampus) could best account for the data (model 8: xp = 0.43, mean variance explained = 6.63%; model 9: xp = 0.57, mean variance explained = 10.22%), though there was no clear winner between the two.

Bayesian model averaging (BMA) was then used to calculate weighted model parameters for the winning models within Family 3 (i.e., weighted by the posterior probability or evidence for each model; Stephan et al., 2010). While the hippocampus and vmPFC showed significant bidirectional intrinsic connectivity throughout the scan (for statistics, see Table 1), only the hippocampus to vmPFC connection increased during event construction, $t(31) = 3.67$, $p < .001$, resulting in significant positive effective connectivity overall (i.e., the sum of the

intrinsic and modulatory parameters), $t(31) = 5.17$, $p < .001$ (see Figure 3). In contrast, vmPFC to hippocampus connectivity decreased slightly, though not significantly, during event construction, $t(31) = 1.13$, $p = .27$, resulting in nonsignificant vmPFC-hippocampus coupling overall, $t(31) = .42$, $p = .68$ (see Figure 3).

TABLE 1 BMA results: Weighted model parameters

	Mean (Hz)	SD (Hz)	t (31)	p
Intrinsic connectivity (A)				
vmPFC to Hip	**0.16**	**0.11**	**8.73**	**<.00001**
Hip to vmPFC	**0.37**	**0.24**	**8.71**	**<.00001**
Modulation by imagination (B)				
Hip to vmPFC	**1.08**	**1.66**	**3.67**	**<.001**
vmPFC to Hip	−0.26	1.32	1.13	.27
Driving input (C)				
All Onsets Hip	0.02	0.20	0.58	.56
All Onsets vmPFC	**−0.19**	**0.34**	**3.19**	**<.01**
Rating phase inputs (C)				
Imag Rate Hip	**−0.07**	**0.14**	**2.65**	**.01**
Obj Rate Hip	0.03	0.12	1.47	.15
Imag Rate vmPFC	**−0.25**	**0.40**	**3.54**	**.001**
Obj Rate vmPFC	**0.22**	**0.29**	**4.19**	**<.001**

Note. Results shown in bold survive FDR correction.
Abbreviations: vmPFC = ventromedial prefrontal cortex, Hip = hippocampus, Imag = Imagine trials, Obj = Object trials.
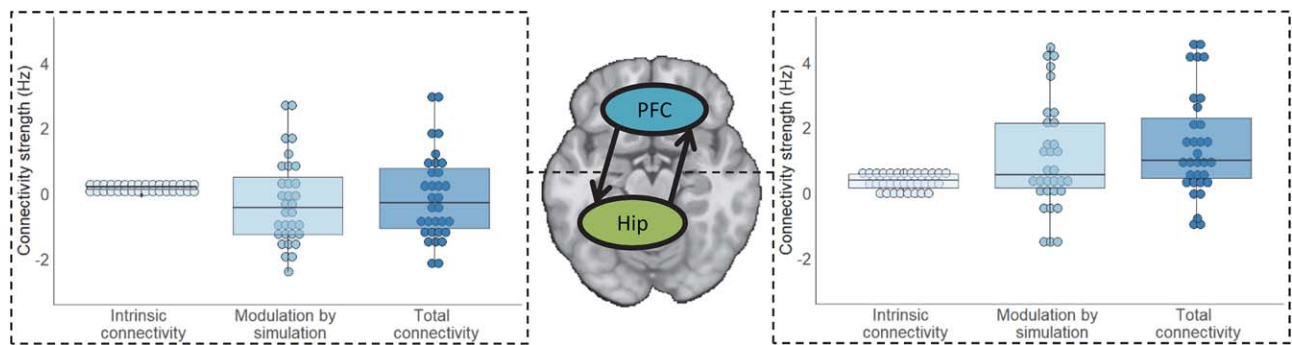
FIGURE 3 Graphic illustration of weighted model parameters. Dots represent individual parameter estimates, with boxplots overlaid. Total connectivity = intrinsic connectivity + modulation by simulation [Color figure can be viewed at wileyonlinelibrary.com]

Taken together, these results suggest that on average there is strong bidirectional coupling between the hippocampus and vmPFC, but only the hippocampus to vmPFC connection increases during initial event construction. This fits well with previous work showing that activity in the hippocampus precedes that in the mPFC in rats during context-guided retrieval (Place et al., 2016)[2] and in humans during autobiographical memory construction (McCormick et al., 2015). However, we cannot conclude from these results that the hippocampus is somehow more critical to episodic simulation than the vmPFC, which some have suggested (Kurczek et al., 2015), as clearly the hippocampus outputs to the vmPFC. Rather, it seems that the hippocampus initiates retrieval of episodic details, which are then integrated within the vmPFC, and these integrated representations may subsequently constrain further retrieval by the hippocampus (for a model of bidirectional hippocampal-mPFC interactions, see Preston & Eichenbaum, 2013). Alternatively, retrieved episodic details may be conveyed to the vmPFC, where they activate associated schematic representations that may then constrain further retrieval and construction processes (Benoit et al., 2014; van Kesteren et al., 2012).

This study contributes to a growing body of work suggesting that hippocampal-vmPFC interactions are critical to a number of memory and imagination functions (Andrews-Hanna, Reidler, Huang, & Buckner, 2010; Brown et al., 2016; Ritchey et al., 2015; Zeithamova et al., 2012). Going forward it will be important to determine the cognitive factors that influence effective connectivity between these regions. For instance, is such connectivity modulated by recombinatorial demands (Gaesser et al., 2013), novelty of the simulated event (Szpunar, Jacques, Robbins, Wig, & Schacter, 2014), or self-relevance of the retrieval cues (D'Argembeau et al., 2010; Szpunar et al., 2009)? In our experiment, generic word cues were used (e.g., Apple, Car, Newspaper), which may have placed particular demands on hippocampally mediated retrieval mechanisms. We might expect more vmPFC to hippocampus connectivity if the cues are personally familiar (Benoit et al., 2014) or relate to particular situational schema (van Kesteren et al., 2012). Finally, we only examined two nodes within the larger core network and the possibility remains that the inclusion of additional nodes (including the right hippocampus) would have changed the overall connectivity pattern including the strength of these connections. Future work should aim to incorporate more regions to determine how information flows within the rest of the system and how it might change at different points during episodic future simulation (e.g., McCormick et al., 2015; St Jacques, Kragel, & Rubin, 2011).

NOTES

[1] However, it should be noted that the same winning models are obtained if DCM analyses are performed on the control and specificity induction data separately.

[2] However, caution should be exercised when drawing parallels between the animal and human literatures, given pronounced anatomical differences particularly in frontal regions.

ORCID

Karen L. Campbell [ID] http://orcid.org/0000-0003-0015-6307

Preston P. Thakral [ID] http://orcid.org/0000-0001-6603-6186

Daniel L. Schacter [ID] http://orcid.org/0000-0002-2460-6061

REFERENCES

Addis, D. R., Wong, A. T., & Schacter, D. L. (2007). Remembering the past and imagining the future: Common and distinct neural substrates during event construction and elaboration. *Neuropsychologia*, *45*, 1363–1377.

Andrews-Hanna, J. R., Reidler, J. S., Huang, C., & Buckner, R. L. (2010). Evidence for the default network's role in spontaneous cognition. *Journal of Neurophysiology*, *104*, 322–335.

Andrews-Hanna, J. R., Reidler, J. S., Sepulcre, J., Poulin, R., & Buckner, R. L. (2010). Functional-anatomic fractionation of the brain's default network. *Neuron*, *65*, 550–562.

Benoit, R. G., & Schacter, D. L. (2015). Specifying the core network supporting episodic simulation and episodic memory by activation likelihood estimation. *Neuropsychologia*, *75*, 450–457.

Benoit, R. G., Szpunar, K. K., & Schacter, D. L. (2014). Ventromedial prefrontal cortex supports affective future simulation by integrating distributed knowledge. *Proceedings of National Academy of Sciences U S A*, *111*, 16550–16555.

Bertossi, E., Tesini, C., Cappelli, A., & Ciaramelli, E. (2015). Ventromedial prefrontal damage causes a pervasive impairment of episodic memory and future thinking. *Neuropsychologia*, *90*, 12–24.

Brown, T. I., Carr, V. A., LaRocque, K. F., Favila, S. E., Gordon, A. M., Bowles, B., … Wagner, A. D. (2016). Prospective representation of navigational goals in the human hippocampus. *Science*, *352*, 1323–1326.

Campbell, K. L., Grigg, O., Saverino, C., Churchill, N., & Grady, C. L. (2013). Age differences in the intrinsic functional connectivity of default network subsystems. *Front Aging Neuroscience*, *5*, 73.

D'Argembeau, A., Stawarczyk, D., Majerus, S., Collette, F., Van der Linden, M., Feyers, D., ... Salmon, E. (2010). The neural basis of personal goal processing when envisioning future events. *Journal of Cognitive Neuroscience*, *22*, 1701–1713.

Demblon, J., Bahri, M. A., & D'Argembeau, A. (2016). Neural correlates of event clusters in past and future thoughts: How the brain integrates specific episodes with autobiographical knowledge. *Neuroimage*, *127*, 257–266.

Friston, K. J. (2011). Functional and effective connectivity: A review. *Brain Connect*, *1*, 13–36.

Friston, K. J., Harrison, L., & Penny, W. (2003). Dynamic causal modelling. *Neuroimage*, *19*, 1273–1302.

Gaesser, B., Spreng, R. N., McLelland, V. C., Addis, D. R., & Schacter, D. L. (2013). Imagining the future: Evidence for a hippocampal contribution to constructive processing. *Hippocampus*, *23*, 1150–1161.

Kurczek, J., Wechsler, E., Ahuja, S., Jensen, U., Cohen, N. J., Tranel, D., & Duff, M. (2015). Differential contributions of hippocampus and medial prefrontal cortex to self-projection and self-referential processing. *Neuropsychologia*, *73*, 116–126.

Madore, K. P., Szpunar, K. K., Addis, D. R., & Schacter, D. L. (2016). Episodic specificity induction impacts activity in a core brain network during construction of imagined future experiences. *Proceedings of National Academy of Sciences U S A*, *113*, 10696–10701.

Martin, V. C., Schacter, D. L., Corballis, M. C., & Addis, D. R. (2011). A role for the hippocampus in encoding simulations of future events. *Proceedings of National Academy of Sciences U S A*, *108*, 13858–13863.

McCormick, C., St-Laurent, M., Ty, A., Valiante, T. A., & McAndrews, M. P. (2015). Functional and effective hippocampal-neocortical connectivity during construction and elaboration of autobiographical memory retrieval. *Cerebral Cortex*, *25*, 1297–1305.

Moscovitch, M., Cabeza, R., Winocur, G., & Nadel, L. (2016). Episodic memory and beyond: The hippocampus and neocortex in transformation. *Annual Review of Psychology*, *67*, 105–134.

Penny, W. D., Stephan, K. E., Daunizeau, J., Rosa, M. J., Friston, K. J., Schofield, T. M., & Leff, A. P. (2010). Comparing families of dynamic causal models. *PLoS Computational Biology*, *6*, e1000709.

Place, R., Farovik, A., Brockmann, M., & Eichenbaum, H. (2016). Bidirectional prefrontal-hippocampal interactions support context-guided memory. *Natural Neuroscience*, *19*, 992–994.

Preston, A. R., & Eichenbaum, H. (2013). Interplay of hippocampus and prefrontal cortex in memory. *Currents Biology*, *23*, R764–R773.

Ritchey, M., Libby, L. A., & Ranganath, C. (2015). Cortico-hippocampal systems involved in memory and cognition: The PMAT framework. In S. O'Mara & M. Tsanov (Eds.), *Progress in brain research* (Vol. *219*, pp. 45–64). Amsterdam, The Netherlands, Oxford, UK, Waltham, MA: Elsevier.

Schacter, D. L., Addis, D. R., & Szpunar, K. K. (2017). Escaping the past: Contributions of the hippocampus to future thinking and imagination. In D. E. Hannula & M. C. Duff (Eds.), *The hippocampus from cells to systems: Structure, connectivity, and functional contributions to memory and flexible cognition* (pp. 439–465). New York: Springer.

Schacter, D. L., Benoit, R. G., & Szpunar, K. K. (2017). Episodic future thinking: Mechanisms and functions. *Currents Opinion in Behavior Science*, *17*, 41–50.

St Jacques, P. L., Kragel, P. A., & Rubin, D. C. (2011). Dynamic neural networks supporting memory retrieval. *Neuroimage*, *57*, 608–616.

Stephan, K. E., Penny, W. D., Moran, R. J., den Ouden, H. E. M., Daunizeau, J., & Friston, K. J. (2010). Ten simple rules for dynamic causal modeling. *Neuroimage*, *49*, 3099–3109.

Szpunar, K. K., Chan, J. C. K., & McDermott, K. B. (2009). Contextual processing in episodic future thought. *Cerebral Cortex*, *19*, 1539–1548.

Szpunar, K. K., Jacques, P. L. S., Robbins, C. A., Wig, G. S., & Schacter, D. L. (2014). Repetition-related reductions in neural activity reveal component processes of mental simulation. *Social Cognitive Affect Neuroscience*, *9*, 712–722.

Thakral, P. P., Benoit, R. G., & Schacter, D. L. (2017). Imagining the future: The core episodic simulation network dissociates as a function of timecourse and the amount of simulated information. *Cortex*, *90*, 12–30.

van Kesteren, M. T. R., Ruiter, D. J., Fernández, G., & Henson, R. N. (2012). How schema and novelty augment memory formation. *Trends in Neuroscience*, *35*, 211–219.

Zeithamova, D., Dominick, A. L., & Preston, A. R. (2012). Hippocampal and ventral medial prefrontal activation during retrieval-mediated learning supports novel inference. *Neuron*, *75*, 168–179.