



Published in final edited form as:

*Hippocampus*. 2018 February ; 28(2): 76–80. doi:10.1002/hipo.22812.

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

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### 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 (fMRI) while they imagined future events in response to object cues. We then used dynamic causal modeling (DCM) 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

imagination; hippocampus; ventromedial prefrontal cortex; fMRI; dynamic causal modeling

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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 et al., 2017b). 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 et al., 2015; Kurczek et al., 2015; Schacter et al., 2017a). Neuroimaging studies suggest that hippocampal activity tracks with the level of retrieval or recombinatorial demand (cf. Gaesser et al., 2013; Thakral et al., 2017). In contrast, vmPFC activity is stronger when the elements of a simulated event are more familiar (Szpunar et al., 2009; Benoit et al., 2014) 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 (Van Kesteren et al., 2012; Benoit et al., 2014; Demblon et al., 2016).

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 et al., 2010b; Campbell et al., 2013), and dynamically interact to support memory and imagination functions (Zeithamova et al., 2012; Ritchey et al., 2015; Brown et al., 2016). 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 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 non-episodic control task (see Figure 1; data from Madore et al., 2016, see that paper for fMRI acquisition and preprocessing 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 6mm 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 et al., 2007; Martin et al., 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 and colleagues (2016) to provide 6 runs of task data per subject (thus maximizing our power)<sup>1</sup>. 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).

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<sup>1</sup>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.

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 et al., 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: 1) *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), 2) *modulatory parameters* reflecting context-dependent changes in connectivity between regions (in this case, connections altered on imagination trials), and 3) *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 et al., 2015; Place et al., 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 et al., 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 2s after cue onset on imagination trials; see Figure 2). All models had bidirectional intrinsic connections between the 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 non-significant vmPFC-hippocampus coupling overall,  $t(31) = .42$ ,  $p = .68$  (see Figure 3).

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)<sup>2</sup> 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 (Van Kesteren et al., 2012; Benoit et al., 2014).

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 et al., 2010a; Zeithamova et al., 2012; Ritchey et al., 2015; Brown et al., 2016). 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 et al., 2014), or self-relevance of the retrieval cues (Szpunar et al., 2009; D'Argembeau et al., 2010)? 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., St Jacques et al., 2011; McCormick et al., 2015).

## Acknowledgments

This research was supported by National Institute of Mental Health Grant MH060941 to D. L. Schacter and a Tier 2 Canada Research Chair to K. L. Campbell.

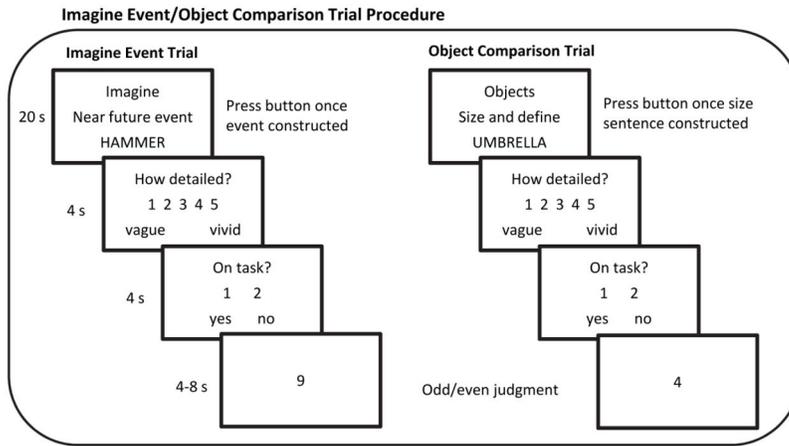
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<sup>2</sup>However, caution should be exercised when drawing parallels between the animal and human literatures, given pronounced anatomical differences particularly in frontal regions.

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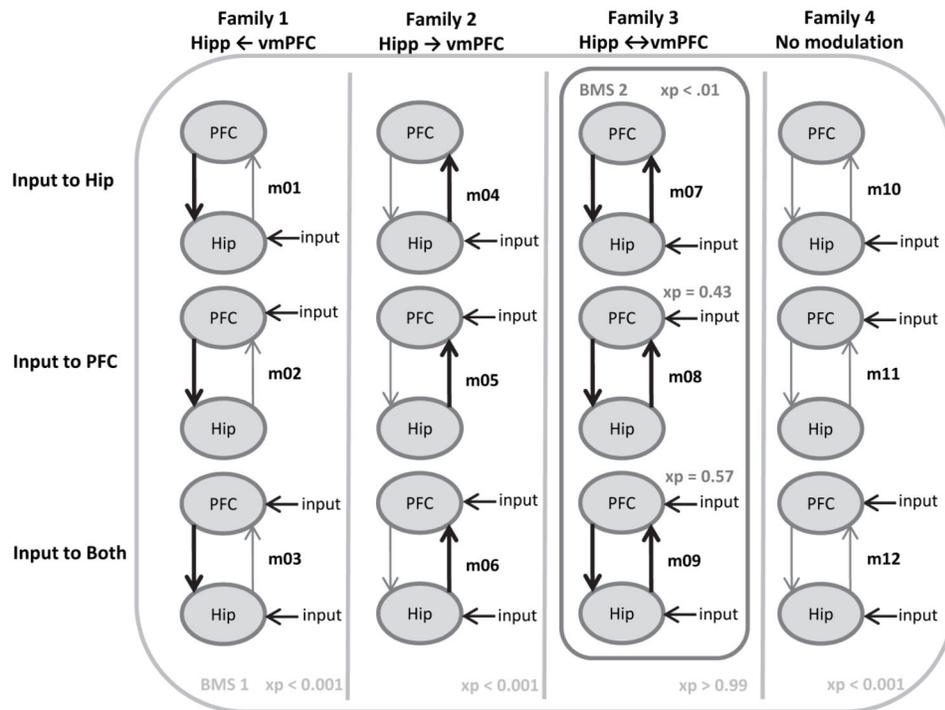
**Figure 1.** Overview of experimental procedure. On *Imagine* trials, participants were instructed to silently generate a novel future event that related to the cue, that was detailed, plausible, specific to one place and time, and viewed from a field perspective. They pressed a button once the event 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.

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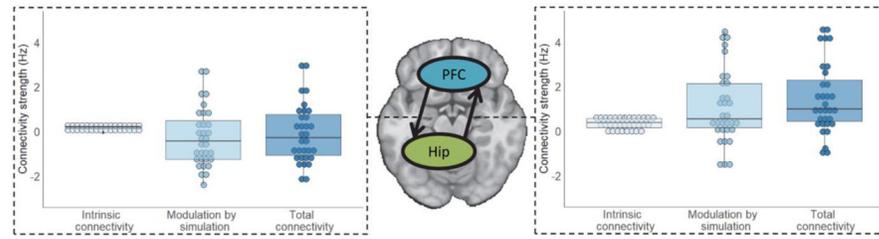
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**Figure 2.** Model specification. Models are divided into 4 families, differing in the modulatory effect of imagination (shown along top and with bold arrows). Within each family, models differ based on where driving inputs enter the system (shown along left-hand side). Exceedance probabilities ( $x_p$ ) for BMS 1 (i.e., at the family level) are shown for each family at the bottom of the figure, whereas  $x_p$ 's for models within the winning family are shown in the column for Family 3.



**Figure 3.**

Graphic illustration of weighted model parameters. Dots represent individual parameter estimates, with boxplots overlaid. Total connectivity = intrinsic connectivity + modulation by simulation.

**Table 1****BMA Results: Weighted Model Parameters**

|                               | <b>Mean (Hz)</b> | <b>SD (Hz)</b> | <b>t (31)</b> | <b>p</b>           |
|-------------------------------|------------------|----------------|---------------|--------------------|
| Intrinsic connectivity [A]    |                  |                |               |                    |
| vmPFC to Hip                  | <b>0.16</b>      | <b>0.11</b>    | <b>8.73</b>   | <b>&lt; .00001</b> |
| Hip to vmPFC                  | <b>0.37</b>      | <b>0.24</b>    | <b>8.71</b>   | <b>&lt; .00001</b> |
| Modulation by imagination [B] |                  |                |               |                    |
| Hip to vmPFC                  | <b>1.08</b>      | <b>1.66</b>    | <b>3.67</b>   | <b>&lt; 0.001</b>  |
| vmPFC to Hip                  | -0.26            | 1.32           | 1.13          | 0.27               |
| Driving input [C]             |                  |                |               |                    |
| All Onsets Hip                | 0.02             | 0.20           | 0.58          | 0.56               |
| All Onsets vmPFC              | <b>-0.19</b>     | <b>0.34</b>    | <b>3.19</b>   | <b>&lt;0.01</b>    |
| Rating phase inputs [C]       |                  |                |               |                    |
| Imag Rate Hip                 | <b>-0.07</b>     | <b>0.14</b>    | <b>2.65</b>   | <b>0.01</b>        |
| Obj Rate Hip                  | 0.03             | 0.12           | 1.47          | 0.15               |
| Imag Rate vmPFC               | <b>-0.25</b>     | <b>0.40</b>    | <b>3.54</b>   | <b>.001</b>        |
| Obj Rate vmPFC                | <b>0.22</b>      | <b>0.29</b>    | <b>4.19</b>   | <b>&lt;0.001</b>   |

Note. Results shown in bold survive FDR correction. vmPFC = ventromedial prefrontal cortex, Hip = hippocampus, Imag = Imagine trials, Obj = Object trials.