Journal Club

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Neural Mechanisms Underlying Schemas and Inferences

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Review of Spalding et al.

If you were shown a picture of two adults with two children, you might infer that they are a family. That relational structure, family, binds these individuals together and helps you remember the individual members better in the future. It can also be applied to other groups of individuals you see, as these relationships generalize across many examples that you have likely encountered before, and do not depend on any particular exemplar. “Family” is a schema, an abstract concept we impose on the world to understand it better. Schemas enable the inference of new information that goes beyond what is directly observed. For example, if you now see an elderly individual together with one of the adults from the photo, you might guess that this person is a grandparent of the children.

The ventromedial prefrontal cortex (vmPFC) is thought to have a key role in retrieving and monitoring information based on schematic associations (Hebscher and Gilboa, 2016). Damage to the vmPFC sometimes causes confabulation symptoms, in which patients describe erroneous, and sometimes fantastical, events and facts with the full conviction of genuine memories (Moscovitch and Melo, 1997). Furthermore, vmPFC damage di-

minishes the memory-enhancing properties of schematic associations (Warren et al., 2014; Spalding et al., 2015). However, it is less clear whether vmPFC is also critical for the fundamental work of schema construction: building bridges between items in memory with shared associations.

In a recent article in *The Journal of Neuroscience*, Spalding et al. (2018) investigated the necessity of the vmPFC in a simple type of schematic memory: associative inference between items in a triad (ABC). People with bilateral vmPFC damage and matched healthy control subjects studied overlapping associations between pairs of common objects (AB and BC), along with unrelated nonoverlapping pairs of objects (XY). Critically, items A and C are linked through a common association with B, but never appeared together. This associative structure results in a hidden relationship that subjects had to infer later. The participants first studied AB pairs and their memory for the association that was tested (with feedback), using a three-alternative forced-choice paradigm, in which they were asked to identify the item that was paired with the target item from three possible choices. Participants then studied and were tested on BC and XY pairs. Each pair was both studied and tested twice. Finally, participants were tested on the unstudied AC pair, as well as being tested again on AB, BC, and XY pairs.

The authors found that individuals with vmPFC damage performed comparably to healthy control subjects for studied (direct association) pairs, with both

groups identifying the correct item paired with the test item on average 77–81% of the time for the first exposure, and almost perfectly (>95% accuracy) at the second exposure. However, the performance of the vmPFC group was impaired for the unstudied, inferred AC pair, with this group only identifying the correct item 48% of the time, compared with the control group identification of 76%. This deficit in inferred pairs was still present after controlling for the memory of direct associate pairs, by only examining the inference relationship in the direct associate pairs that the participants successfully remembered. This well controlled and simple test provided some of the clearest evidence yet that human vmPFC has a necessary role in building schematic associations.

The results of this study complement earlier fMRI findings that activity changes during learning in the vmPFC, along with the hippocampus, are correlated with successful subsequent inference (Zeithamova et al., 2012). However, the specific contributions of the vmPFC and hippocampus to this process remain unclear. Hippocampus and vmPFC damage both impair associative inference while sparing direct associative memory in rodents (Bunsey and Eichenbaum, 1996; Dusek and Eichenbaum, 1997; DeVito et al., 2010). A recent study (Pajkert et al., 2017) in patients with medial temporal lobe damage using a similar associative inference paradigm produced the same pattern of deficit. Thus, damage to both structures disrupts associative inference in seemingly the same way, posing a

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challenge for elucidating the precise roles of the structures.

One key distinction in the contributions of these regions may be the precise timing of when each is necessary for the inference process. Schlichting and Preston (2015) proposed that the hippocampus reactivates memories via pattern completion, a fast associative process in which memories are activated by stimuli that shared features with a prior experience. In contrast, vmPFC serves to abstract a less detailed schematic model later on. This hypothesis was supported by fMRI evidence showing that successful inference after single-trial learning correlated with greater hippocampal engagement, while successful inference after interleaved repetitions of AB and BC pairs coupled with increasing vmPFC and decreasing hippocampal engagement (Zeithamova and Preston, 2010; Zeithamova et al., 2012). These results were taken to indicate that the subsequent repetitions of the pairs (seeing AB for a second time after learning about BC) allows an abstracted schematic representation to form in the vmPFC, while decreasing the need for rapid hippocampal binding. In the study by Spalding et al. (2018), AB and BC pairs were both shown twice, but in a non-interleaved manner, leaving it unclear how much the inference process in the present study depends on pattern completion in the hippocampus versus the slower abstracted schema process in the vmPFC. It is notable that vmPFC patients perform worse than healthy control subjects, but nonetheless their performances are above chance (i.e., 33% in a three-alternative task) in their identification of the AC inference, so it is possible that the intact hippocampus compensated for impaired vmPFC performance via the fast-binding, pattern-completion process. A way to dissociate the two processes would be to test patients with vmPFC damage using the single-trial version of the paradigm, in which the vmPFC would presumably not yet be required, to see whether their performance is intact (Zeithamova and Preston, 2010).

fMRI evidence in the study by Zeithamova et al. (2012) also argues that it is the interaction between vmPFC and hippocampus that is crucial to the formation of schematic associations. However, the necessity of this interaction for associative inference remains untested. This question could be answered by a crossed disconnection study in an animal model, in which the hippocampus and the ventro-

medial prefrontal cortex would be unilaterally lesioned in different hemispheres. This procedure would leave these areas functionally disconnected by ensuring the loss of any intrahemispheric communication, while also preserving a functioning vmPFC and hippocampus in each hemisphere. If associative inference is impaired in these animals to a greater extent than a control lesion group with unilateral vmPFC and hippocampal lesions to the same hemisphere, then it can be concluded that the interaction between the two structures is key to this cognitive process.

The results of the study by Spalding et al. (2018) are of particular interest because they have direct relevance to prominent theories of vmPFC function. Inferences are critical to model-based learning, that is, the ability to detect and represent the latent (i.e., unobserved) causal structure of the environment (Wilson et al., 2014). Without such an ability, we would not be able to act in a proactive and flexible way to advance our interests. Both schematic memory and model-based learning require the same process: the abstraction of a pattern from individual events, and the ability to infer new information from what is only partially observed. Unlike the triad relationship in the current study, however, model-based accounts of learning depend on less well defined features, such as the changes in the history of stimulus–reward associations to determine the current “state,” or context, of the task (Wilson et al., 2014). The model-based theory predicts that the vmPFC is especially critical when the stimulus features appear the same as in the past, but the stimulus–reward relationship has changed because of the shift in state (as in reversal learning, or devaluation). A mechanistic account of how the vmPFC converts information about hidden relationships within a task environment into a meaningful schematic representation of state space is vital to understanding how this region might contribute to model-based learning.

Spalding et al. (2018) provide a valuable contribution in showing that the vmPFC in humans is critical to the simplest form of an associative inference. In doing so, they go beyond previous results that have shown that vmPFC damage disrupts schematic inferences at more complex levels of cognition, and clarifies that vmPFC is necessary to schematic memory formation at a fundamental level. Thus, the findings add to a growing understand-

ing of the neural circuitry involved in the formation of complex memory structures, with critical implications for understanding other processes like learning and decision-making that depend on such schematic representations.

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