Cortex, in press

The status of semantic memory in medial temporal lobe amnesia varies with demands on

scene construction

Kristin Lynch<sup>1,2</sup>, Margaret M Keane<sup>1,3</sup>, and Mieke Verfaellie<sup>1,2</sup>

<sup>1</sup> Memory Disorders Research Center, VA Boston Healthcare System

<sup>2</sup>Boston University School of Medicine

<sup>3</sup> Wellesley College

Correspondence Address: Mieke Verfaellie, Ph.D. Memory Disorders Research Center (151A) VA Boston Healthcare System 150 S Huntington Avenue Boston MA 02130 verf@bu.edu

#### Abstract

Semantic memory is typically preserved in medial temporal lobe (MTL) amnesia. However, there are instances of impairment, such as in the recall of semantic narratives. As some forms of semantic knowledge play out in a spatial context, one possible explanation is that semantic memory impairments, when observed, relate to demands on scene construction – the ability to bind and maintain spatial information in a coherent representation. To investigate whether semantic memory impairments in MTL amnesia can be understood with reference to a deficit in scene construction, the current study examined knowledge of scripts that vary in the extent to which they play out in a scene context in nine patients with MTL amnesia and eighteen healthy control subjects. Scripts are routine activities characterized by an ordered set of actions, including some that are essential for completing the activity. Comparing performance on scene-based scripts (e.g., buying groceries at the grocery store) and object-based scripts (e.g., addressing a letter), we found that patients generated the same number of total action steps as controls for both types of script, but patients were selectively impaired at generating essential actions steps for scene-based scripts. Furthermore, patients made more sequencing and idiosyncratic errors than controls in the scene-based, but not in the object-based, scripts. These findings demonstrate that the hippocampus plays a critical role in the retrieval of semantic knowledge about everyday activities when such retrieval entails scene construction.

*Keywords*: semantic memory, scripts, scene construction, amnesia, medial temporal lobe

# The Status of Semantic Memory in Medial Temporal Lobe Amnesia Varies with Demands on Scene Construction

A core feature of medial temporal lobe (MTL) amnesia is the preservation of semantic memory – conceptual world knowledge not tied to specific episodes (Tulving, 1972). Patients with amnesia perform normally on tests assessing remotely acquired semantic knowledge of objects, facts, and word meanings (Schmolck et al., 2002; Steinvorth et al., 2005). These findings suggest that, once consolidated, semantic memory no longer depends on the hippocampus, being supported instead by neocortical structures (Squire & Alvarez, 1995; Squire & Zola, 1998). There are, however, instances of semantic memory impairment in MTL amnesia. Amnesic patients produce fewer details than control subjects when asked to describe issues in the public domain (e.g., relating to the environment or politics) that were relevant in a specified past time period (Race, Keane, & Verfaellie, 2013) and when recalling well-known semantic narratives (Rosenbaum et al., 2009; Verfaellie, Bousquet, & Keane, 2014). Here, we entertain the possibility that these impairments relate to demands on scene construction.

Evidence suggests that the ability to bind and maintain spatial information into a coherent representation (i.e., scene construction) is impaired in MTL amnesia (Maguire & Mullally, 2013; Mullally & Maguire, 2014). Although not a universal finding (Squire et al., 2010; Kim et al., 2015), amnesic patients have shown impairment in imagining spatially coherent scenes (Hassabis et al., 2007; Mullally, Intraub, & Maguire, 2012) and show reduced boundary extension (wherein individuals extrapolate beyond the actual borders of a scene when recalling that scene; Mullally, et al., 2012). Patients also have

shown impairment in judging whether scene stimuli are structurally possible (McCormick et al., 2017). Given that scenes constitute the context within which events unfold, it has been suggested that impaired retrieval of episodic memories in amnesia also fundamentally reflects impaired scene construction (Hassabis & Maguire, 2007; Clark & Maguire, 2016). The question arises whether deficient semantic memory, when observed, can similarly be understood as the consequence of impaired scene construction.

Semantic memory is typically devoid of spatial context, even when the retrieved information is spatial in nature. For example, remembering that Paris is the capital of France does not require one to construct a scene or setting. Indeed, performance on tasks that tap well-consolidated semantic memory has been shown to be independent of the hippocampus (for review, see Winocur & Moscovitch, 2011). Yet, other kinds of semantic knowledge – such as knowledge of scripts –may play out in a spatial (albeit abstracted) context. For instance, accurate recall of the steps involved in checking out a library book may require one to generate the setting within which the task takes place. To date, knowledge of scripts has been studied primarily in patients with frontal lobe lesions (e.g., Godbout and Doyon, 1995; Zanini, 2008; Allain et al., 2010) and these studies have not considered demands on scene-construction.

To examine whether the status of semantic memory in amnesia differs depending on the degree to which retrieval of that knowledge entails scene construction, we evaluated script knowledge in patients with MTL amnesia. Scripts constitute stereotyped knowledge of routine activities and are characterized by an ordered and hierarchical set of actions (Bower, Black, & Turner, 1979). Scripts differ in the degree to which they unfold in a scene context (e.g., buying groceries at the grocery store vs. addressing a

letter), thereby varying in the degree to which they rely on scene construction. Here, we compared patients' descriptions of scripts that do or do not require scene construction with those of control subjects, and hypothesized that patients would be selectively impaired in generating scene-based scripts.

#### Methods

We report how we determined sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

#### **Participants**

The study sample included 10 amnesic patients (three female) with MTL lesions and 18 healthy control subjects (nine female). Sample size was determined based on prior amnesia studies of semantic memory (Verfaellie, et al., 2014) and script generation (Duff, et al., 2008). Data for one patient who did not follow instructions were excluded. Table 1 presents demographic and neuropsychological data for the remaining nine patients. Etiology of amnesia included hypoxic-ischemic injury, stroke, encephalitis, and status epilepticus followed by left temporal lobectomy. Lesions for seven of the nine patients are presented in Figure 1. Two patients (P4, P6), who had suffered cardiac arrest, could not be scanned due to contraindications. MTL pathology for these patients was inferred from etiology and neuropsychological profile.

Volumetric data for the hippocampus and MTL cortices (Table 1) was available for five patients (P2, P3, P5, P7, P9) who had research scans, using methodology reported elsewhere (Kan, Giovanello, Schnyer, Makris, & Verfaellie, 2007). Volumetric analyses

of the hippocampus and surrounding MTL cortices as a whole revealed that 4 patients had normal parahippocampal gyrus volume but significant hippocampal volume loss. The fifth patient (P2) had lesions extending beyond the MTL into anterolateral temporal neocortex. The CT scan of another patient (P1) also indicated a lesion that included the hippocampus and MTL cortices. For the patient with encephalitis (P8), clinical MRI was acquired in the acute phase of illness, and whereas the T1-weighted images showed no visible lesions, T2-flair images revealed bilateral hyperintensities in the MTL and anterior insula.

Control subjects were matched to the patient group for age (M = 57.83), education (M = 15.17), and verbal intelligence as measured by the Wechsler Adult Intelligence Scale, Third Edition (M = 107.11). All participants provided informed consent in accordance with the Institutional Review Boards at Boston University and the VA Boston Healthcare System.

#### Materials

Eight common activities (scripts) were used as stimuli, of which four were "object-based" (*writing a check, making a peanut butter and jelly sandwich, wrapping a present, making tea*) and four "scene-based" (*going to the grocery store, taking a bus, borrowing a library book, eating at a restaurant*). These scripts were selected from a larger set based on ratings from pilot studies. In one pilot study, participants (n = 26) provided ratings (from 1 to 5) of the degree to which they focused (1) primarily on the object(s) involved in the task, and (2) more broadly on the scene or spatial environment in which the task takes place. The four object-based scripts received high object ratings (M = 4.52) and low scene ratings (M = 2.01). The four scene-based scripts received high

scene ratings (M = 4.33) and low object ratings (M = 2.63). The two types of scripts were matched for familiarity (mean scene-based = 4.10, mean object-based = 4.07), as determined in a separate pilot study (n = 50). In that study, participants listed the steps involved in each script and then rated script familiarity. To generate a list of acceptable action steps for each script, two independent raters determined which steps in participants' script descriptions constituted actions relevant to completing that activity. Action steps that were given by 60% of pilot participants were considered essential action steps (i.e., necessary for task completion). Inter-rater reliability was calculated using data from six subjects for the eight scripts using free-marginal Kappa; values ranged from 0.85 to 0.95.

#### Procedure

For each script, participants were asked to generate aloud the sequence of steps involved in completing the activity as though they were "writing out an instruction manual – a step-by-step list of instructions – for someone who has never done the task before." After completing a practice script (*starting a fire in the fireplace*), participants were given three minutes to complete each of eight test scripts. Script order was randomized for each participant, with the stipulation that the first and second set of four scripts contained two scene-based and two object-based scripts. Two control participants received the same script order as each patient.

At the end of the task, the experimenter probed participants' approach to each script. Participants were asked whether they simply knew the steps involved in the activity or pictured the activity, and if the latter, whether they thought about a specific instance in the past. If participants indicated picturing a specific instance, their approach was considered episodic; otherwise it was considered semantic.

#### Scoring

The eight scripts were scored both for the number of acceptable and essential action steps. Participants were given credit for an action step if they stated the step explicitly or gave a step that was similar enough to imply a clear understanding that the step is required for the task. For example, a patient provided the following step for the script *eating at a restaurant*: "You'll get to pick, usually the salad comes first." While not explicitly matching the action step "Order food," this response nonetheless indicates a clear understanding that ordering food is a required component of eating at a restaurant. A primary rater scored all scripts for action steps and essential action steps, and a secondary rater scored 15% of the scripts. Cronbach's alpha showed high inter-rater reliability ( $\alpha = .99$ ).

Scripts were also scored for the number of sequencing errors, idiosyncratic responses, and repetitions (see Appendix for examples). Sequencing errors were instances in which the order of an action was abnormal or impossible. Because the script "writing a check" has no fixed sequence, this script was excluded from the analysis of sequencing errors. Idiosyncratic responses were instances where an action reflected personal style and could not be generalized to others. Repetitions were instances where an action was repeated unnecessarily. Neither idiosyncratic responses nor repetitions were included in the total number of action steps.

#### Data analysis

We compared the number of essential action steps and total action steps in the two groups separately for scene-based and object-based scripts. Next, we compared the number of errors and repetitions across groups. Nonparametric tests (Mann-Whitney Utests) were used, as the assumption of normality was violated and variances across groups were unequal.

No part of the study procedures or analyses was pre-registered prior to the research being undertaken. Experimental data are available at osf.io/z6jex.

#### Results

For scene-based scripts, amnesic patients generated marginally fewer essential action steps than did controls (median 2.50 vs. 3.38, respectively; U = 44.5, p = .059; Table 2). There was no significant difference between amnesic patients and controls in total action steps (U = 52, p = .136). For object-based scripts, there was no significant difference between amnesic patients and controls in either essential (U = 76.5, p = .815) or total action steps (U = 55, p = .180).

To further clarify whether there was a selective impairment for scene-based scripts, we examined group differences in the number of essential action steps for scene-based scripts while covarying for the number of essential action steps for object-based scripts. A rank analysis of covariance (Quade, 1967) revealed a significant group effect, F(1, 25) = 5.29, p = .03, indicating that amnesic patients were selectively impaired in generating essential action steps in scene-based scripts.<sup>1</sup> A similar result was obtained

<sup>&</sup>lt;sup>1</sup> Results did not change when analyses were repeated excluding the amnesic patient whose lesion includes the anterolateral temporal region.

when limiting the analysis to patients with restricted hippocampal lesions, F(1, 20) = 5.36, p = .031.

Because one of the scene-based scripts elicited nearly twice the overall number of action steps in controls compared to each of the others (median for restaurant was 13, compared to 8 for grocery, 6 for bus, and 7 for library), we reanalyzed the data with that script excluded. Patients again generated fewer essential action steps than did controls (median 2.33 vs. 3.17, respectively; U = 40, p = .033), whereas there was no difference in the total number of action steps (median 5.67 vs. 7.00; U = 62, p = .326). A rank covariance analysis controlling for the number of essential steps for object-based scripts again revealed a significant effect of group, F(1,25) = 6.62, p = .016.

Patients made significantly more sequencing errors than control subjects in scenebased scripts (U = 119, p = .029), but not in object-based scripts (U = 85, p = .651). Patients had significantly more idiosyncratic responses than control subjects in scenebased scripts (U = 112.5, p = .016), but not in object-based scripts (U = 77.5, p = .771). Groups did not differ in number of repetitions for either scene-based (U = 79, p = .909) or object-based scripts (U = 61.5, p = .192).

Finally, both groups primarily used a semantic approach (Table 3). There was no difference between the groups in how frequently they relied on a semantic (vs. episodic) approach to generate either scene-based,  $\chi^2(1, N = 97) = 2.71$ , p = .10, or object-based activities,  $\chi^2(1, N = 97) = 0.06$ , p = .81.

Discussion

Amnesic patients with MTL lesions and control subjects were asked to generate the steps involved in completing common object-based and scene-based activities. Although they generated the same number of total action steps as controls for both object-based and scene-based scripts, the amnesic patients, including those with lesions limited to the hippocampus, were selectively impaired at generating essential action steps for scene-based scripts. Furthermore, amnesic patients made more sequencing errors and gave more idiosyncratic responses than controls in the scene-based scripts. These results are in line with our hypothesis that patients would be selectively impaired at retrieving semantic knowledge about everyday activities when such retrieval entails scene construction.

Because a scene anchors the unfolding of action steps, the failure to generate a scene may also be responsible for the observation that patients generated more sequencing errors than controls for scene-based scripts. Interestingly, the increase in sequencing errors for scene-based scripts may provide an explanation for the paradoxical finding that total action steps for scene-based scripts were not reduced in amnesic patients, even though essential action steps were. That is, an action step generated out of sequence may provide an additional cue to generate extra steps related to that action that would otherwise be omitted. For example, one patient provided the following sequence of steps for the script *eating at a restaurant*: pay the check, eat your meal somewhere in there, drink your tea. The action step *eat your meal somewhere in there* was given out of sequence, which may have prompted the patient to generate the extra action step, *drink your tea*. For the script *going to the grocery store*, a patient gave the following sequence of steps: get the receipt, charge it, sign. Here, the out-of-sequence step *charge it* may

have cued the patient to generate the extra action step *sign*. These extra action steps may have been omitted if not for the action steps generated out of sequence. Thus, an inability to construct the scene in which an activity unfolds may lead to the presence of sequence errors, which in turn may mask an impairment in total action steps.

Inherently, scene-based and object-based scripts may differ in other theoretically relevant ways. By its nature, a routine activity centered on an object in isolation entails a more restricted focus, not only in space but also in time. In contrast, by virtue of their more expansive scope, scene-based scripts entail actions that unfold across space and time. Could our results reflect the differential temporal extent of scene-based in comparison to object-based scripts? Interestingly, St-Laurent et al. (2011) argued that MTL patients have reduced temporal resolution in their description of autobiographical memories. As object-based scripts may in fact require finer temporal resolution than the scene-based scripts, which are more extended in time, such an impairment would be expected to lead to poorer temporal sequencing of object-based compared to scene-based scripts. It is not clear, however, that the argument from St-Laurent et al. (2011) is applicable in the present study, owing to the fact that the former study explicitly probed for detail whereas our study did not.

Another consequence of the more expansive scope of scene-based scripts is that they may contain more (or more salient) event boundaries than object-based scripts, thus yielding greater segmentation of the unfolding action. Given the role of the hippocampus in retrieving information across event boundaries (Swallow et al., 2011), this raises the possibility that amnesics' impairment in generating essential action steps in scene-based scripts could be due to a failure to engage hippocampal mechanisms for retrieving actions

that are separated across boundaries. Notably, Magliano and Zacks (2011) have demonstrated that it is action discontinuities rather than spatiotemporal discontinuities that primarily drive event-segmentation. \_Action boundaries can be identified either based on pre-existing knowledge structures or on the basis of sensory input about movement features (Zacks, 2004). Because our study involved generation of action steps rather than observation of an unfolding action, movement features cannot be captured. However, participants' generation of discrete steps corresponds to action discontinuities as defined by their underlying knowledge structure. Notably, the average number of essential action steps for the scene-based scripts (excluding the restaurant script) was no different from that for the object-based scripts (means = 5.33 vs. 5.25). Thus, there is no evidence in the present study that the selective impairment for scene-based scripts is due to a difference in the way actions in scene- and object-based scripts are segmented.

Another way in which scene-based and object-based scripts may differ is with regard to the constraint they place on possible action steps, as well as on the unfolding of these steps in sequence. In the domain of autobiographical memory, it has been postulated that the degree of open-endedness of a retrieval task determines hippocampal involvement (Sheldon and Levine, 2016). Extending this postulate to semantic memory, if scene-based scripts are indeed more open-ended, this could provide an alternative interpretation for the selective impairment for scene-based scripts in the amnesic group. One measure of the open-endedness of a script is the number of steps generated that do not qualify as essential. These are action steps that showed less overlap across participants in the pilot study, such that they were not provided by at least 60% of participants. Indeed, when all scene-based scripts were considered, control subjects

provided more non-essential action steps (calculated as the difference between total and essential action steps) for scene-based than for object-based scripts. However, this was no longer the case when the restaurant script was eliminated from the analysis. That is, in the follow up analysis, the number of non-essential action steps in the control group was equivalent across object- and scene-based scripts<sup>2</sup>. Critically, amnesic patients still showed a selective impairment in generating essential action steps for the scene-based scripts, even though these scripts were now equated for open-endedness with the object-based scripts.

Our findings go beyond those of St-Laurent et al. (2009) who examined script generation in patients with temporal lobe epilepsy. Finding an impairment in patients post-lobectomy but not in those pre-lobectomy, they concluded that script generation depends on anterolateral temporal cortex, as this region remains intact in pre-surgery patients but is resected in post-surgery patients. Our findings demonstrate an additional role for the MTL, and in particular the hippocampus, in the generation of scripts that are scene-based. Our results differ from those of Duff et al. (2008) who reported intact script generation (including generation of essential steps) in patients with hippocampal lesions. However, only three scripts were included in their study, two of which are arguably object-based (*making a sandwich* and *changing a tyre* [sic]). Furthermore, the scene-based script (*buying groceries in an American supermarket*) contained only three essential steps, limiting sensitivity of the measure. The present study highlights the importance of considering the role of scene construction when assessing the status of semantic memory retrieval in MTL amnesia.

<sup>&</sup>lt;sup>2</sup> Eliminating the restaurant script, the median number of non-essential action steps in the control group was 3.88 for object-based scripts and 3.83 for scene-based scripts.

Our results are consistent with neuroimaging findings of semantic memory retrieval involving spatial information, a key component of scene construction. Ryan et al. (2010) demonstrated that the hippocampus is preferentially engaged in semantic memory when the task requires retrieval of spatial vs. non-spatial relations. Likewise, in Hoscheidt et al. (2010), the hippocampus was activated during the retrieval of both episodic and semantic memories that entail a spatial component.

Whereas our study focused on the retrieval of verbal semantic information, impaired scene construction has also been posited as an explanation for impaired navigation in a well-known environment. Maguire et al. (2006) found that a licensed London taxi driver with hippocampal amnesia was able to navigate effectively in London when the route consisted of major roadways, but became lost when navigation relied on the complex system of smaller roadways. The authors interpreted this finding as an impairment in scene construction, manifested as an inability to visualize precisely where to turn off major roadways onto smaller roadways. This interpretation was bolstered by the finding that the same patient was impaired at imagining fictitious scenes (Hassabis et al., 2007).

In the same vein, scene construction may facilitate performance in other semantic memory tasks in which patients generated less detail than controls (Rosenbaum et al., 2009; Race et al., 2013; Verfaellie, Bousquet, & Keane, 2014). For instance, when recounting fairy tales, although gist information may be accessible independent of its spatial context, retrieval of more fine-grained detail may require a read-out of details that become available by virtue of the scene(s) in which the narrative unfolds. Thus, impaired

scene construction in amnesia may account for these instances of impaired semantic memory.

Yet, the contribution of scene construction to semantic memory is not limited to instances that require detail generation, as the current study found an impairment in the generation of essential elements. Knowledge of scripts is not typically represented in verbal form; rather, its retrieval requires the translation of action knowledge into verbal form – actions that, in the case of scene-based scripts, unfold in a specific spatial context. One might ask whether the need to enact the unfolding of an activity might evoke episodic memory, thus providing an alternative means to generate relevant action steps. By this interpretation, patients' impairment would be a consequence of their impaired episodic memory rather than impaired scene construction. This interpretation is unlikely. There is no a priori reason to suspect that episodic memory would make a greater contribution to scene-based than to object-based script generation. In fact, ratings obtained in this study demonstrate that participants were no more likely to rely on episodic memory for scene-based than for object-based scripts. Moreover, there was no difference among patients and controls in their reported use of an episodic strategy.

There are several limitations of the study that should be acknowledged. As in many studies of patients with MTL amnesia, the sample size was modest, necessitating the use of nonparametric statistics and covariate analysis to explore the interaction. Additionally, the number of essential action steps, ranging between four and seven across scripts, was restricted, potentially limiting the sensitivity not only of the number of essential action steps, but also of sequencing errors. Nonetheless, the current results provide novel evidence pertaining to the role of the hippocampus in semantic memory.

Prior work has highlighted hippocampal contributions to semantic memory in the context of semantic memory tasks in which episodic memory processes may be invoked to enhance performance (e.g., Westmacott et al., 2004; Greenberg et al., 2009; Sheldon, Romero & Moscovitch, 2013). The present results go further by demonstrating that a hippocampally mediated process, namely scene construction, is mandatory for the expression of certain kinds of semantic knowledge. Such results are not easily accommodated by current theories of semantic memory postulating that remote semantic memories are supported solely by structures outside of the hippocampus (Winocur & Moscovitch, 2011; Squire & Alvarez, 1995). Rather, they suggest that the neural basis of semantic memory varies depending on the extent to which scene construction contributes to the retrieval of knowledge. Our findings agree with the notion that the process of scene construction is hippocampally mediated (Maguire and Mullally, 2013), regardless of whether it occurs in the service of episodic or semantic memory.

### Acknowledgements

This research was supported by NIH grant #R01MH093431, the Clinical Science Research and Development Service, Department of Veterans Affairs, and by a Brachman Hoffman Award from Wellesley College to M.K. These funding sources had no involvement in the conduct of the research or the preparation of the manuscript. The authors have no competing interests to declare.

The authors thank Dr. Daniel Greenberg for helpful discussion about this work, and Kathryn Bousquet, Michelle Lee, Renee Hunsberger, and Aubrey Wank for research assistance. The contents of this manuscript do not represent the views of the U. S. Department of Veterans Affairs or the United States Government. References

- Allain, P., Le Gall, F., Etcharry-Bouyx, Aubin, G, & Emile, J. (1999). Mental representation of knowledge following frontal-lobe lesion: Dissociations on tasks using scripts. *Journal of Clinical and Experimental Neuropsychology*, 21, 643-665. https://www.tandfonline.com/doi/abs/10.1076/jcen.21.5.643.871
- Bower, G. H., Black, J. B., & Turner, T. J. (1979). Scripts in memory for text. *Cognitive Psychology*, *11*, 177–220. https://doi.org/10.1016/0010-0285(79)90009-4
- Clark, I. A., & Maguire, E. A. (2016). Remembering preservation in hippocampal amnesia. Annual Review of Psychology, 67, 51–82. https://doi.org/10.1146/annurev-psych-122414-033739
- Duff, M. C., Hengst, J. A., Tengshe, C., Krema, A., Tranel, D., & Cohen, N. J. (2008). Hippocampal amnesia disrupts the flexible use of procedural discourse in social interaction. *Aphasiology*, 22, 866–880. https://doi.org/10.1080/02687030701844196
- Godbout, L., & Doyon, J. (1995). Mental representation of knowledge following frontallobe or postrolandic lesions. *Neuropsychologia*, 33, 1671-1696. https://doi.org/10.1016/0028-3932(95)00047-X
- Greenberg, D. L., Keane, M. M., Ryan, L. & Verfaellie, M. (2009). Impaired category fluency in medial temporal lobe amnesia: The role of episodic memory. *Journal* of Neuroscience, 29, 10900-10908. https://doi.org/10.1523/JNEUROSCI.1202-09.2009
- Hassabis, D., Kumaran, D., Vann, S. D., & Maguire, E. A. (2007). Patients with hippocampal amnesia cannot imagine new experiences. *Proceedings of the*

*National Academy of Sciences*, *104*, 1726–1731. https://doi.org/10.1073/pnas.0610561104

- Hassabis, D., & Maguire, E. A. (2007). Deconstructing episodic memory with construction. *Trends in Cognitive Sciences*, *11*, 299–306.
  https://doi.org/10.1016/j.tics.2007.05.001
- Hoscheidt, S. M., Nadel, L., Payne, J., & Ryan, L. (2010). Hippocampal activation during retrieval of spatial context from episodic and semantic memory. *Behavioural Brain Research*, 212, 121–132. https://doi.org/10.1016/j.bbr.2010.04.010
- Kan, I. P., Giovanello, K. S., Schnyer, D. M., Makris, N., & Verfaellie, M. (2007). Role of the medial temporal lobes in relational memory: Neuropsychological evidence from a cued recognition paradigm. *Neuropsychologia*, 45, 2589–2597. https://doi.org/10.1016/j.neuropsychologia.2007.03.006
- Kim, S., Dede, A. J. O., Hopkins, R. A., & Squire, L. R. (2015). Memory, scene construction, and the human hippocampus. *Proceedings of the National Academy* of Sciences, USA, 112, 15, 4767-4772. https://doi.org/10.1073/pnas.1503863112
- Magliano, J. P. & Zacks, J. M. (2011). The impact of continuity editing in narrative film on event segmentation. *Cognitive Science*, 35, 1489–1517. https://doi.org/10.1111/j.1551-6709.2011.01202.x

Maguire, E. A., & Mullally, S. L. (2013). The hippocampus: A manifesto for change.
 *Journal of Experimental Psychology: General*, 142, 1180–1189.
 https://doi.org/10.1037/a0033650

- Maguire, E. A., Nannery, R., & Spiers, H. J. (2006). Navigation around London by a taxi driver with bilateral hippocampal lesions. *Brain*, 129, 2894–2907. https://doi.org/10.1093/brain/awl286
- McCormick, C., Rosenthal, C. R., Miller, T. D., & Maguire, E. A. (2017). Deciding what is possible and impossible following hippocampal damage in humans. *Hippocampus*, 27, 303–314. https://doi.org/10.1002/hipo.22694
- Mullally, S. L., Intraub, H., & Maguire, E. A. (2012). Attenuated boundary extension produces a paradoxical memory advantage in amnesic patients. *Current Biology*, 22, 261–268. https://doi.org/10.1016/j.cub.2012.01.001
- Mullally, S. L., & Maguire, E. A. (2014). Memory, imagination, and predicting the future: A common brain mechanism? *The Neuroscientist*, 20, 220–234. https://doi.org/10.1177/1073858413495091
- Quade, D. (1967). Rank analysis of covariance. *Journal of the American Statistical Association*, 62, 1187–1200. https://doi.org/10.1080/01621459.1967.10500925
- Race, E., Keane, M. M., & Verfaellie, M. (2013). Losing sight of the future: Impaired semantic prospection following medial temporal lobe lesions. *Hippocampus*, 23, 268–277. https://doi.org/10.1002/hipo.22084
- Rosenbaum, R. S., Gilboa, A., Levine, B., Winocur, G., & Moscovitch, M. (2009).
  Amnesia as an impairment of detail generation and binding: Evidence from personal, fictional, and semantic narratives in K.C. *Neuropsychologia*, 47, 2181–2187. https://doi.org/10.1016/j.neuropsychologia.2008.11.028

- Ryan, L., Lin, C.-Y., Ketcham, K., & Nadel, L. (2010). The role of medial temporal lobe in retrieving spatial and nonspatial relations from episodic and semantic memory. *Hippocampus*, 20, 11–18. https://doi.org/10.1002/hipo.20607
- Schmolck, H., Kensinger, E. A., Corkin, S., & Squire, L. R. (2002). Semantic knowledge in patient H.M. and other patients with bilateral medial and lateral temporal lobe lesions. *Hippocampus*, *12*, 520–533. https://doi.org/10.1002/hipo.10039
- Sheldon, S. & Levine, B. (2016). The role of the hippocampus in memory and mental construction. Annals of the New York Academy of Sciences, 1369, 76-92. https://doi.org/10.1111/nyas.13006
- Sheldon, S., Romero, K., & Moscovitch, M. (2013). Medial temporal lobe amnesia impairs performance on a free association task. *Hippocampus*, 23, 405-412. https://doi.org/10.1002/hipo.22099
- Squire, L. R., & Alvarez, P. (1995). Retrograde amnesia and memory consolidation: A neurobiological perspective. *Current Opinion in Neurobiology*, *5*, 169-177. https://doi.org/10.1016/0959-4388(95)80023-9
- Squire, L. R., van der Horst, A. S., McDuff, S. G., Frascino, J. C., Hopkins, R. O., & Mauldin, K. N. (2010). Role of the hippocampus in remembering the past and imagining the future. *Proceedings of the National Academy of Sciences*, USA, 107, 19044-19048. https://doi.org/10.1073/pnas.1014391107

Squire, L. R., & Zola, S. M. (1998). Episodic memory, semantic memory and amnesia. *Hippocampus*, 8, 205-211. https://doi.org/10.1002/(SICI)1098-1063(1998)8:3<205::AID-HIPO3>3.0.CO;2-I Steinvorth, S., Levine, B., & Corkin, S. (2005). Medial temporal lobe structures are needed to re-experience remote autobiographical memories: Evidence from H.M. and W.R. *Neuropsychologia*, 43, 479–496. https://doi.org/10.1016/j.neuropsychologia.2005.01.001

St-Laurent, M., Moscovitch, M., Levine, B., & McAndrews, M. P. (2009). Determinants of autobiographical memory in patients with unilateral temporal lobe epilepsy or excisions. Neuropsychologia, 47, 2211–2221. https://doi.org/10.1016/j.neuropsychologia.2009.01.032

St-Laurent, M., Moscovitch, M., Tau, M., and McAndrews, M. P. (2011). The temporal unraveling of autobiographical memory narratives in patients with temporal lobe epilepsy or excisions. *Hippocampus*, 21, 409-421. https://doi.org/10.1002/hipo.20757

Swallow, K. M., Barch, D. M., Head, D., Mayley, C. J., Holder, D., & Zacks, J. M. (2011). Changes in events alter how people remember recent information. *Journal* of Cognitive Neuroscience, 23, 1052-1064.

https://doi.org/10.1162/jocn.2010.21524

Tulving, E. (1972). Episodic and semantic memory. In *Organization of Memory* (pp. 381-403). Oxford, England: Academic Press.

Verfaellie, M., Bousquet, K., & Keane, M. M. (2014). Medial temporal and neocortical contributions to remote memory for semantic narratives: Evidence from amnesia. *Neuropsychologia*, 61, 105–112.

https://doi.org/10.1016/j.neuropsychologia.2014.06.018

- Westmacott, R., Black, S. E., Freedman, M., & Moscovitch, M. (2004) The contribution of autobiographical significance to semantic memory: Evidence from Alzheimer's disease, semantic dementia, and amnesia. *Neuropsychologia*, 42, 25-48. https://doi.org/10.1016/S0028-3932(03)00147-7
- Winocur, G., & Moscovitch, M. (2011). Memory transformation and systems consolidation. *Journal of the International Neuropsychological Society*, *17*, 766– 780. https://doi.org/10.1017/S1355617711000683
- Zachs, J. M. (2004). Using movement and intentions to understand simple events. *Cognitive Science*, 28, 979-1008. https://doi.org/10.1016/j.cogsci.2004.06.003
- Zanini, S. (2008). Generalized script sequencing deficits following frontal lobe lesions. *Cortex*, 44, 140-149. https://doi.org/10.1016/j.cortex.2006.03.002

# **Figure Caption**

Figure 1. Structural MRI and CT scans depicting medial temporal lobe (MTL) lesions for 7 of the 9 amnesic participants. The left side of the brain is displayed on the right side of the image. CT slices show lesion location for P1 in the axial plane. T1-weighted MRI images depict lesions for P2, P3, P5, and P7 and P9 in the coronal plane. T2-flair MRI images depict lesion locations for P8 in the axial plane.

Figure 1



Patient	Etiology	Age	Edu	WAI	S-III	WMS III			Volume Loss (%)		
	(ye		(years)	VIQ	WMI	GM	VD	AD	Hippocampal	Subhippocampal	
P1	Hypoxic ischemic	65	12	88	75	52	56	55	N/A	N/A	
P2	Status epilepticus + left temp. lobectomy	51	16	93	94	49	53	52	63%	60% <sup>a</sup>	
P3	Hypoxic ischemic	59	14	106	115	59	72	52	22%	_	
P4	Hypoxic ischemic	63	17	131	126	86	78	86	N/A	N/A	
P5	Stroke	62	18	117	88	67	75	55	62%	_	
P6	Hypoxic ischemic	65	16	100	88	86	78	83	N/A	N/A	
P7	Hypoxic ischemic	47	12	103	95	59	68	55	46%	_	
P8	Encephalitis	73	13	99	104	49	56	58	N/A	N/A	
P9	Stroke	51	20	111	99	60	65	58	43%	_	

Table 1. Demographic, Neuropsychological and Neurological Characteristics of Amnesic Participants

Note. WAIS-III = Wechsler Adult Intelligence Scale, Third Edition; WMS-III = Wechsler Memory Scale, Third Edition; VIQ = verbal intelligence quotient; WMI = working memory index; GM = general memory; VD = visual delayed; AD = auditory delayed; N/A = not available.

<sup>a</sup> Volume loss in left anterior parahippocampal gyrus (i.e., entorhinal cortex, medial portion of the temporal pole, and the medial portion of perirhinalcortex; see Kan et al., 2007, for methodology)

	Scene	-Based Sc	ripts	<b>Object-Based Scripts</b>			
	Median	Mean	SD	Median	Mean	SD	
Action Steps							
Essential Steps							
Patients	2.50	2.56	1.04	4.25	3.56	1.11	
Controls	3.38	3.29	1.00	4.00	3.78	0.75	
Total Steps							
Patients	7.50	7.00	2.02	6.50	6.53	2.23	
Controls	8.13	8.49	2.25	7.88	7.79	1.79	
Sequencing Errors							
Patients	0.25	0.28	0.23	0.00	0.03	0.08	
Controls	0.00	0.13	0.26	0.00	0.02	0.08	
Idiosync. Responses							
Patients	0.00	0.11	0.13	0.00	0.06	0.17	
Controls	0.00	0.01	0.06	0.00	0.06	0.14	
<u>Repetitions</u>							
Patients	0.00	0.17	0.22	0.00	0.03	0.08	
Controls	0.00	0.19	0.26	0.00	0.12	0.18	

Table 2. Performance in script generation task

	Scene-	Based Sci	ripts	<b>Object-Based Scripts</b>			
	Median	Mean	SD	Median	Mean	SD	
Task Approach							
Semantic							
Patients	1.00	0.81	0.27	1.00	0.92	0.18	
Controls	1.00	0.92	0.12	1.00	0.93	0.12	
Episodic							
Patients	0.00	0.19	0.28	0.00	0.08	0.18	
Controls	0.00	0.08	0.12	0.00	0.07	0.12	

Table 3. Proportion of scripts for which an episodic/semantic approach was endorsed

# Appendix

## Examples of different error types

Sequencing error

- *Going to the grocery store:* Put the groceries in the car; bring them home; bring a pen with me to cross items off list.
- *Taking a bus:* Pull in to Port Authority; get off bus; make sure you have belongings.

Idiosyncratic error

- *Making a Peanut Butter and Jelly sandwich:* You could put everything on cold and then put [the PB&J sandwich] in the microwave.
- *Going to the grocery store:* Go up and down the aisles; check things off on list; try not to impulse buy too much.

## Repetition

- *Taking a bus*: You put money in the coin collector, although I suppose now you can slide your bankcard. You put the money in the money collector.
- *Making tea:* As soon as it's boiling, pour water over the teabag; heat the cup for the tea; put the teabag in; pour water over teabag.

Essential steps for each script

Borrowing library book

Search for book in catalogue/computer Get location/call number information Find book on shelf and take it Bring book to circulation desk Check book out

Going to restaurant

Order drinks Read menu Order food Waiter brings food Eat food Ask for check Pay for bill

Going to grocery store

Entering store Get cart or basket Locate/pick up items Go to cash register Pay

Taking a bus

Wait at bus stop Bus arrives Get on the bus Sit or stand Ride, watch, and wait for stop Get off the bus

Making a peanut butter and jelly sandwich Get two bread slices Spread peanut butter with knife Spread jelly Combine slices

Making a cup of tea

Fill kettle with water Turn on stove Heat the teakettle/put teakettle on the stove Wait for water to boil Put teabag in cup Pour water in mug

# Let steep

Wrapping a present

Estimate size of paper needed Put box on wrapping paper Cut paper Use tape

Writing a check

Write date on check Fill in recipient line Write number for dollar amount Write amount in words Add memo Sign check