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Losing Sight of the Future: Impaired Semantic Prospection Following Medial Temporal Lobe Lesions

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ABSTRACT: The ability to imagine the future (prospection) relies on many of the same brain regions that support memory for the past. To date, scientific research has primarily focused on the neural substrates of episodic forms of prospection (mental simulation of spatiotemporally specific future events); however, little is known about the neural substrates of semantic prospection (mental simulation of future nonpersonal facts). Of particular interest is the role of the medial temporal lobes (MTLs), and specifically the hippocampus. Although the hippocampus has been proposed to play a key role in episodic prospection, recent evidence suggests that it may not play a similar role in semantic prospection. To examine this possibility, amnesic patients with MTL lesions were asked to imagine future issues occurring in the public domain. The results showed that patients could list general semantic facts about the future, but when probed to elaborate, patients produced impoverished descriptions that lacked semantic detail. This impairment occurred despite intact performance on standard neuropsychological tests of semantic processing and did not simply reflect deficits in narrative construction. The performance of a patient with damage limited to the hippocampus was similar to that of the remaining patients with MTL lesions and amnesic patients' impaired elaboration of the semantic future correlated with their impaired elaboration of the semantic past. Together, these results provide novel evidence from MTL amnesia that memory and prospection are linked in the semantic domain and reveal that the MTLs play a critical role in the construction of detailed, multi-element semantic simulations. © **2012 Wiley Periodicals, Inc.**

KEY WORDS: semantic memory; episodic memory; hippocampus; amnesia; imagination

INTRODUCTION

Humans have a remarkable capacity to disengage from the present moment and mentally project into the future to envision upcoming events and to anticipate future scenarios. Such mental simulation of the future (prospection) consumes nearly one-third of our spontaneous cognition at rest and supports a range of adaptive behaviors, from planning to problem solving (Atance and O'Neill, 2001; Suddendorf and Corballis, 2007; Andrews-Hanna et al., 2010; Peters and Buchel, 2010; Sheldon et al., 2011). Prospection is not a unitary process and can take two different forms: episodic and semantic (Atance and O'Neill, 2001). Episodic prospection refers to the capacity to mentally project oneself into the future to pre-experience a spatiotemporally specific event, such as imagining trying to refuel your car at a gas station during a future oil shortage. Semantic prospection refers to the capacity to imagine facts and general conceptual knowledge free of context and personal significance, such as imagining the effects of future oil shortages on global politics and foreign policy (Klein et al., 2002). A critical question is how the brain supports these two forms of prospection in the service of adaptive behavior.

Recent insight into the neural substrates of episodic prospection has come from the study of neurological patients who have difficulty envisioning events in their personal future, including patients with lesions in the frontal, parietal, temporal lobes, or thalamus (Tulving, 1985; Hassabis et al., 2007b; Andelman et al., 2010; Berryhill et al., 2010; Squire et al., 2010; Race et al., 2011; Weiler et al., 2011), as well as from neuroimaging studies of healthy subjects engaged in future-thinking tasks (Okuda et al., 2003; Addis et al., 2007, 2009; Hassabis et al., 2007a; Botzung et al., 2008). These studies have revealed that many of the same neural structures that support memory for the past also support imagining the future (Buckner and Carroll, 2007; Hassabis and Maguire, 2007; Schacter and Addis, 2007; Schacter et al., 2007; Suddendorf and Corballis, 2007; Spreng and Grady, 2010). Of particular interest has been the potential contribution of the medial temporal lobes (MTLs), and specifically the hippocampus, to episodic prospection (Addis and Schacter, 2011). Although common hippocampal activity has been observed in neuroimaging studies when subjects remember past events and envision future events, debate continues as to whether processes supported by the MTL are necessary for episodic prospection (Maguire and Hassabis, 2011; Martin et al., 2011; Squire et al., 2011). The findings of intact episodic prospection in amnesic patients with hippocampal lesions suggest that episodic prospection may be supported by cortical regions outside the hippocam-

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pus, such as medial frontal and lateral temporal cortex (Maguire et al., 2010; Squire et al., 2010; Cooper et al., 2011; Hurley et al., 2011). However, other studies have found that amnesic patients with hippocampal damage have difficulty in imagining future events (Hassabis et al., 2007b; Andelman et al., 2010; Kwan et al., 2010; Race et al., 2011) and that the magnitude of patients' prospection deficits correlates with the magnitude of their accompanying deficits in episodic memory (Race et al., 2011). These results favor the alternative hypothesis that episodic memory and prospection both depend on intact hippocampal function.

Interestingly, observations of preserved episodic prospection in hippocampal amnesia have primarily occurred when patients were free to imagine future scenarios of their choice or in cases of developmental amnesia in which hippocampal damage occurred perinatally or in early childhood (Maguire et al., 2010; Squire et al., 2010; Cooper et al., 2011). It has been argued that under such conditions, patients could build simulations of the future by drawing on preserved generalized memory for routine events or well-established scripts in semantic memory (Maguire et al., 2010; Addis and Schacter, 2011; Cooper et al., 2011; Hurley et al., 2011; Maguire and Hassabis, 2011; Race et al., 2011). An intriguing possibility is that hippocampal contributions to prospection depend on the semantic or episodic nature of future thought. Although hippocampal processes may be critical for episodic simulations of the future that primarily draw on episodic memory, hippocampal processes may not be required for semantic simulations of the future that primarily draw on semantic memory.

Currently, little is known about the neural substrates of semantic prospection. Recent studies in patients with semantic dementia or Alzheimer's disease suggest that semantic prospection depends on the integrity of semantic memory systems and brain regions associated with semantic memory storage and retrieval (e.g., the anterior temporal lobes and inferior frontal gyrus; Duval et al., 2012; Irish et al., 2012). It is less clear whether semantic prospection critically depends on MTL function and the integrity of neural systems associated with episodic memory. Selective impairments in episodic future thinking observed in case studies of amnesia have provided preliminary evidence supporting neural distinctions between episodic and semantic forms of prospection (Klein et al., 2002; Andelman et al., 2010). The most widely cited example is the case of patient D.B., who, after suffering hypoxic brain damage, could not imagine events occurring in his personal future (e.g., his next birthday) but retained some ability to imagine future issues occurring in the public domain (e.g., future medical breakthroughs; Klein et al., 2002). The patient demonstrated a similar selectivity in his ability to remember the past, with impaired memory for his personal past (argued to be a metric of episodic memory) but preserved memory for the nonpersonal past (argued to be a metric of semantic memory).

Although these results suggest that semantic simulation of the future can be supported by neural structures that are distinct from those supporting episodic memory, inferences about the differential dependence of these functions on the hippocampus have been limited by the fact that prospection has been probed at a coarser level of detail in the semantic domain (in which tasks require patients simply to list public issues) than in the episodic domain (in which tasks typically require patients to describe events in detail). Of note, common hippocampal activity has recently been observed in a neuroimaging study when healthy subjects envisioned the past and the future in both personal and nonpersonal contexts (Abraham et al., 2008), suggesting that the hippocampus may contribute to both episodic and semantic forms of memory and prospection. An important outstanding question is whether processes supported by the hippocampus are critical for rich mental simulations outside the episodic domain.

To investigate this question, the current study tested whether eight amnesic patients with MTL lesions including the hippocampus (of whom one had neural damage restricted to the hippocampus; see Table 1) could imagine past and future issues occurring in the public domain. A memory and prospection assessment battery was administered in which patients and controls listed general issues relevant to the nonpersonal past and future (e.g., the most important issues faced by the community) following the methods of Klein et al. (2002) when assessing patient D.B. Critically, the current study included an additional elaboration measure to match more closely the procedures used in typical episodic prospection tasks and to assess more thoroughly the content of patients' future thoughts. Specifically, after listing general issues relevant to the nonpersonal past and future, patients and controls were instructed to select one issue and to describe its significance in detail.

MATERIALS AND METHODS

Participants

Eight amnesic patients (three females) with MTL lesions participated in the study (Table 1). To assess the extent of patients' neural damage, structural magnetic resonance imaging (MRI) scans were collected for four of the patients. (MRI could not be obtained for the remaining patients because of medical contraindications; however, MTL pathology can be inferred on the basis of etiology and neuropsychological profile.) Information about the acquisition and analysis of MRI scans and lesion volumetrics has been previously reported (Kan et al., 2007; Race et al., 2011). In terms of MTL pathology, P05 had damage limited to the hippocampus, and P01, P02, and P04 had damage to the hippocampus and surrounding parahippocampal gyrus. The only extra-MTL volume reductions were observed in P02 (right lateral temporal lobe) and P04 (left lateral temporal lobe). No common volume reductions were observed outside the MTL, and the hippocampus was the single structure damaged across all participants.

The neuropsychological profiles of all patients indicate impairments isolated to the domain of memory with extensive impairments in new learning (Table 1). Of importance to the current study, patients performed normally on various tasks of

TABLE 1.

Patient Demographic, Neuropsychological, and Neurological Characteristics

				WAIS III				WMS III				
Patient	Etiology	Age (yr)	Education (yr)	VIQ	Vocabulary	BNT	PPT	GM	VD	AD	WM	Vol loss
P01	Encephalitis	55	14	92	10	53	50	45	56	55	85	73%
P02	Encephalitis	66	12	106	9	50	49	69	68	77	111	66%
P03	Anoxia	60	12	83	8	49	50	52	56	55	91	N/A
P04	Anoxia + left temporal lobectomy	46	16	86	6[a]	43[b]	47	49	53	52	93	63%
P05	Anoxia	54	14	111	10	57	50	59	72	52	96	22%
P06	Encephalitis	82	18	135	17	60	49	45	53	58	141	N/A
P07	Anoxia	58	17	134	17	60	52	70	75	67	126	N/A
P08	Anoxia	60	16	110	14	52	51	62	68	61	92	N/A

WAIS III = Wechsler Adult Intelligence Scale III; VIQ = Verbal IQ; BNT = Boston Naming Test (maximum = 60); PPT = Pyramids and Palm Trees (cutoff = 46); WMS III = Wechsler Memory Scale III; GM = general memory; VD = visual delayed; AD = auditory delayed; WM = working memory; Vol Loss = bilateral hippocampal volume loss.
[a]Borderline impaired.
[b]Impaired.

semantic processing (Boston Naming Test, WAIS III Vocabulary, Pyramids and Palm Trees), with the exception of P04 whose semantic deficits (evident in borderline performance on WAIS III Vocabulary and impaired performance on Boston Naming) were likely due to left anterolateral temporal lobe damage (Schwarz and Pauli, 2009). Data analysis was performed with and without P04, and the inclusion or exclusion of this patient did not affect any of the reported results (see Supporting Information S1 document). The amnesic patients also had documented deficits in episodic prospection (Race et al., 2011).

Twelve healthy controls also participated (six females). The control group was matched to the patient group in terms of mean age (60 yr, SD = 12.2), education (14 yr, SD = 2.0), and verbal IQ (105, SD = 15.7). All participants provided informed consent in accordance with the procedures of the Institutional Review Boards at the Boston University and the VA Boston Healthcare System.

Materials and Procedure

Questionnaires were formed that required participants to describe scenarios in the public domain (e.g., issues facing the environment, issues facing your community, foreign policy/national defense issues, job skills/professions, and discoveries) that were relevant to either the future (in 20 yr) or the past (when you were growing up). Five of the questions referred to the future, and five of the questions referred to the past. Twenty years was selected for the future time frame in an effort to match the temporal distance of past and future issues while remaining within a time frame of plausible life expectancy.

Each scenario was read aloud by the experimenter, one at a time. The participants were first instructed to report the three most important issues relevant to the scenario (e.g., Imagine the presidential election in the year 2032. What will be the three most important foreign policy or national defense issues debated in the election?). The participants were allotted three min for their response; however, they did not have to use the full three min if they produced three issues before time was up or indicated that they were finished. Next, the participants were instructed to choose one of the issues that they had just reported (if they were able to complete the first question) and to describe why that issue will be (or was) important and how it will affect (or affected) people's lives. The participants were again allotted 3 min for each of their responses and continued with their descriptions without interference from the examiner until they came to the end of 3 min or to a natural ending point.

Testing occurred in two sessions in which participants described public issues relevant to the past and the future as well as personal events relevant to the past and the future (data from personal event condition have been reported elsewhere; Race et al., 2011). Trials were blocked by condition (personal/public); however, presentation order of conditions was counterbalanced across sessions and participants. Similarly, within the public issue condition, trials were blocked by temporal direction (future, past), and future issues were always presented prior to past issues to ensure that performance on the prospection trials was not affected by performance on the memory trials. Testing sessions were digitally recorded for subsequent transcription and scoring.

Scoring

Participants were first given a score of 0–3 for the number of issues listed in response to the first probe question. For issue elaboration, participants' narratives were scored using an adapted autobiographical interview scoring procedure (Levine et al., 2002; Race et al., 2011). Each narrative was first segmented into distinct details, and then each detail was

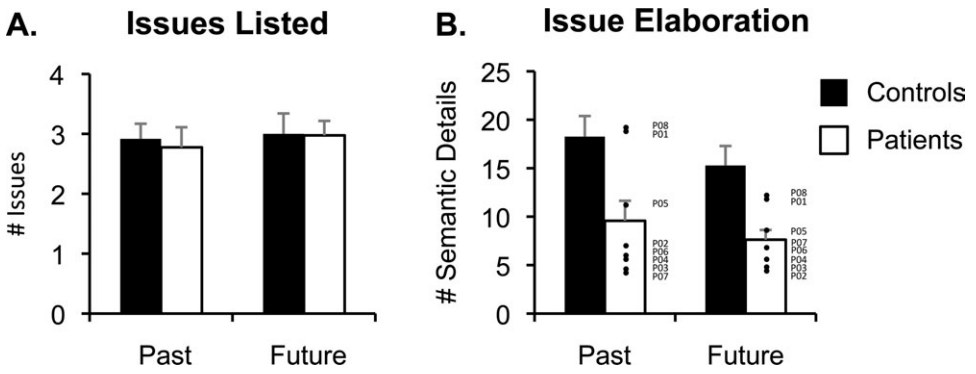

FIGURE 1. Memory and prospection performance. A: Mean number of issues listed by controls (black bars) and amnesic patients (white bars) for each past and future question. B: Mean number of semantic details generated during issue elaboration by the two groups, with individual patient performance superimposed over white bars. Error bars indicate SEM.

categorized as a general (semantic) detail, an external detail, a repetition, or a metacomment about the task. Semantic details included general knowledge and facts, ongoing events and extended states of being, and were further categorized as general semantic, semantic autobiographical, semantic time, and semantic place details. External details included information external to the main issue being described. Although the narratives were semantic in nature, we also included an episodic detail category to allow for the possibility that event-specific details could be present.

For each narrative, the number of details in each category was counted for each subject and averaged across the five issues in the past time period and the five issues in the future time period. Interrater reliability of scoring was established on the basis of 20 narratives scored by two raters (an equal number of future/past and patient/control narratives were scored). Following methods used in prior studies (Levine et al., 2002; Hassabis et al., 2007b; Race et al., 2011), the primary scorer was not blind to subject status, but the second trained scorer was blind to subject status. Intraclass correlation analysis indicated high agreement across scorers for future issues (Cronbach's $\alpha = 0.98$ for total details, $\alpha = 0.97$ for total semantic details) as well as high agreement across scorers for past issues (Cronbach's $\alpha = 0.96$ for total details, $\alpha = 0.91$ for total semantic details).

To verify that subjects in both groups were projecting into the future and the past during the memory and prospection conditions rather than simply describing issues relevant to the present time period, three independent raters blind to subject status scored whether each issue produced by participants was more plausible with respect to the future or the past on a 1–5 scale (1 = uniquely plausible for the past, 5 = uniquely plausible for the future). When these scores were submitted to a 2 × 2 ANOVA with factors of group and temporal direction, a main effect of temporal direction [$F_{(1,8)} = 10.33$, $P = 0.01$] confirmed that temporal plausibility differed for issues produced for the future and the past conditions, with future issues being more plausible for the future (mean rating = 3.3) and past issues being more plausible for the past (mean rating = 2.7). Critically, there was no interaction between group and temporal direction [$F_{(1,8)} = 0.44$, $P = 0.53$], indicating that the differential temporal plausibility of future and past issues did not differ between patients and controls. These results revealed that amnesic and control groups alike were projecting into the future or the past as requested, rather than merely generating issues pertinent to the present.

RESULTS

Performance on the memory and prospection battery is presented in Figure 1. The average number of issues listed for each question (five questions indexing the past and five questions indexing the future) was analyzed by a two-way mixed-factorial ANOVA with factors of group (patient and control) and temporal direction (past and future; Fig. 1A). Patients and controls listed a similar number of issues [$F_{(1,18)} = 0.88$, $P = 0.36$] regardless of whether those issues occurred in the past or in the future [group × temporal direction; $F_{(1,18)} = 0.60$, $P = 0.45$]. In contrast, performance differences between patients and controls emerged during issue elaboration when subjects were required to describe these issues in greater detail (Fig. 1B). During issue elaboration, the majority of details generated by patients and controls were semantic in nature (composed of general knowledge, facts, or extended states of being), with both groups producing on average less than one detail per narrative that was not semantic (e.g., episodic details, repetitions, metacomments about the task, or information external to the main issue being described). Thus, all analyses of issue elaboration were restricted to semantic details.

The patients generated significantly fewer semantic details than controls during issue elaboration (Fig. 1B), as revealed by a main effect of group in a two-way mixed-factorial ANOVA with factors of group and temporal direction [$F_{(1,18)} = 9.36$, $P < 0.01$]. Although participants as a whole produced a greater number of details for past than future issues [main effect of temporal direction; $F_{(1,18)} = 14.55$, $P = 0.05$], the magnitude of patients' impairment did not differ across future and past time periods [group × temporal direction; $F_{(1,18)} = 0.19$, $P = 0.67$]. Follow-up pairwise comparisons indicated that patients

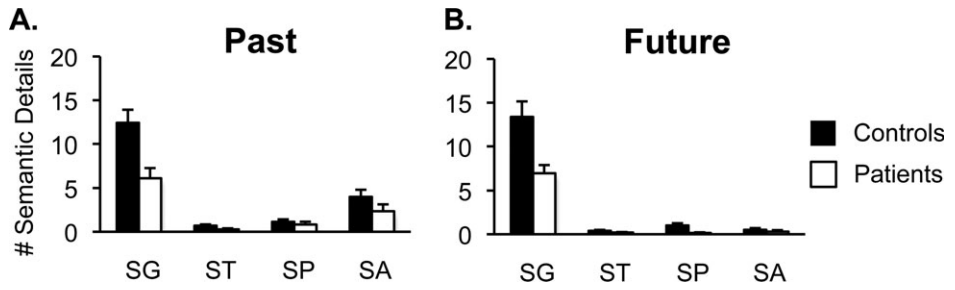

FIGURE 2. Mean number of semantic details generated by controls (black bars) and patients (white bars) in each semantic detail category during (A) past and (B) future issue elaboration. Detail categories: SG, semantic general; ST, semantic time; SP, semantic place, SA, semantic autobiographical. Error bars indicate SEM.

generated fewer semantic details than controls in both the past condition and the future condition (t values > 2.74, P values < 0.05). Example future issues and elaboration narratives from a patient and a control subject are provided in Supporting Information S2 document.

To investigate whether isolated hippocampal damage was sufficient to impair semantic prospection, the performance of the patient with selective hippocampal damage (P05) was separately analyzed and compared with the performance of the remaining patients with MTL lesions using a modified t-test for single cases (Crawford and Howell, 1998). P05 listed a similar number of issues as the remaining patients for both the past condition [$t(6) = 0.51$, $P = 0.31$] and the future condition [$t(6) = 0.35$, $P = 0.37$; Fig. 1A]. During issue elaboration, P05 also produced a similar number of semantic details as the remaining patients for both the past condition [$t(6) = 0.26$, $P = 0.40$] and the future condition [$t(6) = 0.32$, $P = 0.38$; Fig. 1B]. In contrast, P05 produced numerically fewer semantic details when compared with the control group during both past and future issue elaboration; however, this difference was not significant [$t(11) = -0.92$, $P = 0.19$].

To investigate whether the semantic memory and prospection impairments in amnesia reflected general deficits in semantic processing, patient performance was measured on three standard neuropsychological tests of semantic processing (Boston Naming Test, WAIS III Vocabulary, Pyramids and Palm Trees). Patient performance was largely within the normal range on each of these tests (Table 1), and patients' semantic processing performance on these tests did not predict their ability to imagine the semantic future or the semantic past during the elaboration phase of the experiment ($rs < 0.42$, $Ps > 0.30$). The one patient who did demonstrate impairments on two of the semantic processing measures (impaired performance on Boston Naming Test and borderline performance on WAIS III Vocabulary) was P04, whose semantic deficits likely resulted from his left anterolateral temporal lobectomy (Schwarz and Pauli, 2009). However, all main analyses were performed with and without P04, and the inclusion or exclusion of this patient did not affect any of the reported results (see Supporting Information S1 document).

Figure 2 presents the number of details produced within each of four subcategories of semantic detail (semantic general, semantic time, semantic place, and semantic autobiographical) for the past and the future narratives. When data were submitted to a three-way mixed-factorial ANOVA with factors of group (patients vs. controls), temporal direction, and semantic detail category, there was a main effect of detail category [$F_{(3,54)} = 73.71$, $P < 0.001$], with subjects producing more details in the general semantic category than in any other category for future and past issues ($P < 0.001$ for all pairwise comparisons with the general semantic category). Although the extent of patients' impairment differed according to detail category [group $\times$ category interaction; $F_{(3,54)} = 7.86$, $P < 0.01$], patients produced numerically fewer details than controls across each semantic detail category. Follow-up pairwise analyses indicated that this impairment was significant for general semantic and semantic time details ($P < 0.05$). Patient P05's performance was analyzed using a modified t-test for single cases (Crawford and Howell, 1998) and did not differ from that of the remaining patients in any of the semantic detail subcategories [semantic general: $t(6) = 0.34$, $P = 0.37$; semantic time: $t(6) = -0.17$, $P = 0.44$; semantic place: $t(6) = -0.15$, $P = 0.44$; semantic autobiographical: $t(6) = 0.32$, $P = 0.38$]. Like the amnesic group as a whole, P05 produced numerically fewer details than controls in each of the semantic detail categories. However, the reductions that reached significance in the amnesic group as a whole were not significant in P05 [semantic general: $t(11) = -0.95$, $P = 0.18$; semantic time: $t(11) = -0.91$, $P = 0.19$].

To examine the relationship between semantic past and future thought, correlations across tasks were computed. A strong positive correlation was found between the ability to imagine the future (number of semantic details generated during future issue elaboration) and the ability to remember the past (number of semantic details generated during past issue elaboration) in both controls and patients ($r = 0.66$, $P < 0.05$ and $r = 0.94$, $P < 0.001$, respectively), raising the possibility that a common cognitive mechanism underlies both functions. Indeed, the group difference in detail generation in the future condition no longer reached significance after covarying for performance in the past condition [$F_{(1,17)} = 1.32$, $P = 0.27$].

Given the narrative nature of the elaboration phase, it was important to determine whether patients' deficits in semantic prospection during this phase simply reflected deficits in narra-

tive construction or verbal fluency. Although this same group of amnesic patients previously demonstrated preserved ability to construct verbal narratives when describing elements in visually presented pictures (Race et al., 2011), this possibility was investigated by conducting a hierarchical regression on semantic prospection performance (number of semantic details produced during issue elaboration) with narrative construction (picture-narrative performance; Race et al., 2011), performance on the semantic memory task, and group entered as predictors. Narrative construction did not significantly predict semantic future-thinking performance [$R^2 = 0.05$, $F_{(1,18)} = 1.03$, $P = 0.32$], and semantic memory performance continued to predict future-thinking performance when added to the second step of the model [R^2 change= 0.56, $F_{(1,17)} = 24.75$, $P < 0.001$]. Furthermore, adding group to the third step of the model did not improve its capacity to account for variance in future-thinking performance [R^2 change = 0.03, $F_{(1,16)} = 1.38$, $P = 0.26$], indicating that patients' impairments in semantic prospection could not be attributed to group-related factors beyond those accounting for variance in semantic memory performance. Although the results of this regression analysis must be interpreted with caution given our small sample size, it is notable that semantic memory performance significantly predicted future-thinking performance even with this sample size. Furthermore, performance on the picture-narrative task did not correlate with performance on the semantic memory task ($r = 0.26$, $P = 0.27$), and investigation of the collinearity statistics for the model confirmed that the predictors were not collinear and would not prevent accurate estimates of the regression coefficients.

To further investigate whether patients' impairments in semantic prospection were related to potential deficits in spontaneous verbal generativity, an additional hierarchical regression was performed with a measure of verbal fluency (FAS; Benton and Hamsher, 1976) entered as a predictor. Although verbal fluency predicted patients' future-thinking performance [$R^2 = 0.50$, $F_{(1,6)} = 6.03$, $P = 0.05$], adding semantic memory performance to the second step of the model significantly enhanced the model fit [R^2 change = 0.44, $F_{(1,5)} = 37.45$, $P < 0.005$], providing additional evidence from MTL amnesia that memory and prospection are linked in the semantic domain. Collinearity statistics for the model confirmed that the entered predictors were not collinear and would not prevent the model from accurately estimating regression coefficients.

DISCUSSION

In this study, amnesic patients with MTL lesions and healthy controls were asked to imagine future issues occurring in the public domain. Although patients were able to list general issues relevant to future, when probed to elaborate on these issues patients produced impoverished descriptions containing fewer semantic details than those of control participants. This semantic elaboration impairment in amnesia occurred despite intact performance on standard neuropsychological tests of semantic processing. These results challenge the notion that prospection is intact in amnesia when free of spatiotemporal context and personal relevance and suggest that a critical factor determining the status of semantic prospection in amnesia, and MTL contributions to prospection, is the level of detail required by the task. Indeed, prior reports of intact semantic prospection in amnesia have only required patients to imagine the future at a coarse level of detail (Klein et al., 2002; Andelman et al., 2010). The current results revealed that although preserved general conceptual knowledge in amnesia may support semantic prospection to a limited extent, this knowledge is not sufficient to support detailed and specific simulations of the semantic future.

Given that patients' semantic prospection impairments were observed during the elaboration phase of the semantic prospection task, it was important to consider whether these impairments simply reflect deficits in narrative construction. The evidence against this possibility comes from the prior finding that this same group of amnesic patients demonstrated intact ability to construct verbal narratives based on visually presented pictures (Race et al., 2011). In addition, variance in this narrative construction measure did not account for variance in issue elaboration performance in the current study.

In addition to impairments describing public issues relevant to the future, the amnesic group also demonstrated impairments describing public issues relevant to the past. Specifically, although patients were able to list general semantic issues about the past, their elaborations of these issues lacked a richness of semantic detail. Critically, this impairment describing detailed semantic information about the past positively correlated with patients' ability to imagine detailed semantic information about the future. These results suggest a link between memory and prospection in the semantic domain (Suddendorf and Corballis, 2007; Raby and Clayton, 2009) and raise important questions about the nature of the impairment in amnesia that underlies deficits in semantic past and future thought.

One possibility is that the impairments in amnesia reflect more general semantic processing deficits, as is likely the case in patients with semantic dementia (Duval et al., 2012; Irish et al., 2012). However, our amnesic patients performed as well as the control group on tests of semantic processing (Boston Naming Test, WAIS III Vocabulary, Pyramids and Palm Trees) and patients' performance on these measures of semantic processing did not correlate with their performance on the semantic memory or prospection tasks. Although one patient with left lateral temporal lobe damage (P04) did score lower than controls on two of the semantic processing measures (Boston Naming Test, WAIS III Vocabulary), the semantic memory and prospection deficits in amnesia continued to remain significant when this patient was excluded from analysis. Together, these results suggest that the semantic memory and prospection impairments observed in amnesia do not simply reflect general semantic processing deficits.

A second possibility is that the deficits in amnesia reflect impaired semantic memory retrieval processes that reduce

access to conceptual knowledge during past and future thought. In particular, intact MTL function may be required to support generative retrieval processes that provide access to detailed and specific semantic information that is not automatically activated in response to a cuing probe. The evidence in favor of this hypothesis comes from patient and neuroimaging studies that have demonstrated hippocampal involvement in semantic tasks such as free verbal association and semantic category fluency (Maguire and Mummery, 1999; Manns et al., 2003; Burianova and Grady, 2007; Whatmough and Chertkow, 2007; Abraham et al., 2008; Ryan et al., 2008, 2010; Rosenbaum et al., 2009; Smith and Squire, 2009; Whitney et al., 2009; Burianova et al., 2010; Sheldon and Moscovitch, 2012). Hippocampal contributions to semantic retrieval in these tasks have been interpreted in several ways. One proposal is that the hippocampus supports the recovery of spatial information or the creation of spatial contexts that serve as a framework to help generate related semantic details (Ryan et al., 2008, 2010; Sheldon and Moscovitch, 2012). Indeed, healthy controls report using spatial strategies when retrieving items from semantic memory (e.g., visualizing themselves in a kitchen when describing items that belong in a kitchen), and activity has been observed in the hippocampus during category production tasks that specifically elicit spatial retrieval strategies (Ryan et al., 2008). Although subjects in the current study were not required to situate their semantic scenarios in specific spatial contexts, mentally generating such contexts and related spatial information could have facilitated the retrieval of semantic details during past and future issue elaboration. For example, when attempting to imagine the impact of future oil shortages on people's lives, subjects could have benefitted from mentally constructing a scene at a gas station to help generate relevant semantic information.

A complementary explanation for the amnesic impairment in past and future semantic thinking is that generative semantic retrieval during past and future thought normally depends in part on episodic memory, which is compromised in these patients. Specifically, memory processes that support the recovery of autobiographical details may facilitate the retrieval of related semantic information. For example, when attempting to imagine the impact of future oil shortages on people's lives, control subjects may benefit from remembering a specific prior experience that took place during the oil shortage of 1973. Although both patients and controls generated very few episodic details in the current paradigm, it is known that semantic memory and episodic memory are interdependent and that episodic memory can aid the retrieval of semantic knowledge (Barsalou, 1988; Westmacott and Moscovitch, 2003; Ryan et al., 2008; Greenberg and Verfaellie, 2010). Furthermore, neuroimaging studies have demonstrated hippocampal activity when healthy subjects report retrieving autobiographical information to help generate semantic knowledge (Ryan et al., 2008; Sheldon and Moscovitch, 2012), and patients with MTL damage do not benefit from the opportunity to use episodic strategies during semantic retrieval (Greenberg et al., 2009). Although the contribution of the MTL to semantic retrieval may not be limited to its role in episodic memory (Manns et al., 2003), the mental generation of episodic details may be one factor underlying controls' superior performance during semantic elaboration.

In addition to supporting generative retrieval of semantic details, the MTL may also contribute to elaborated past and future thought by virtue of its role in mnemonic binding. More specifically, the hippocampus may support the combination of conceptual details into complex, multi-element representations. This proposal is in line with relational theories of hippocampal function and the proposal that the hippocampus supports the creation of multi-attribute representations by indexing memories stored in neocortex (Eichenbaum and Cohen, 2001; Giovanello et al., 2004; Addis and Schacter, 2011; Wixted and Squire, 2011; Addis et al., 2012). Although more typically associated with episodic memory, these hippocampal binding functions may also be relevant for information processing in the semantic domain. Indeed, hippocampal activity has been observed when subjects retrieve spatial and nonspatial relations from semantic memory (Ryan et al., 2010), and recent electrophysiological evidence suggests that hippocampal activity predicts the spontaneous retrieval of semantically related information during memory search (Manning et al., 2012). Hippocampal binding processes may also contribute to the organization of semantic past and future thought by integrating retrieved semantic details into coherent simulations of the future and the past (Addis and Schacter, 2011). Although the current study did not include a measure of coherence, support for this notion comes from prior studies that have found evidence for reduced coherence in amnesic patients' simulations outside the episodic domain, such as when patients imagine scenes or remember stories (Hassabis et al., 2007b; Rosenbaum et al., 2009). Although the generation of isolated semantic facts may not always depend on hippocampally mediated mnemonic binding functions, these functions may play a critical role when constructing more detailed and complex semantic representations. As such, elaborated constructions of the semantic future and past may be particularly vulnerable to hippocampal damage.

The proposal that hippocampal damage impairs generative semantic retrieval and binding is akin to the proposal that hippocampal damage impairs detail generation and binding in the episodic domain (Addis and Schacter, 2008, 2011; Schacter and Addis, 2009) and may provide a parsimonious explanation for the future-thinking impairments that have been observed in both domains in amnesia. Indeed, a recent neuroimaging study identified common activity in the hippocampus when healthy subjects envisioned both the personal and the nonpersonal future (Abraham et al., 2008), providing support for the notion that episodic prospection and semantic prospection share fundamental underlying cognitive processes supported by the hippocampus. However, an important difference is that although detailed memory retrieval and binding are mandatory for episodic prospection, given its spatiotemporally specific nature, detailed memory retrieval and binding are not mandatory in the semantic domain. Indeed, deficits in episodic simulation

have been observed in amnesia when probed at both the specific (Hassabis et al., 2007b; Race et al., 2011) and the general (Klein et al., 2002; Andelman et al., 2010) levels, and the hippocampus is engaged during episodic prospection both when subjects select single future events to imagine and when subjects elaborate on these events (Addis et al., 2007). In contrast, demands on detailed memory retrieval and binding during semantic prospection may be determined by the nature of the cuing probe, and these processes may not be necessary when semantic prospection is tested at a general level. Such a notion is consistent with the finding that MTL amnesic patients show normal semantic future thinking when required only to generate (but not to elaborate on) single issues (this study; Klein et al., 2002; Andelman et al., 2010).

In light of the absence of volumetric data in some patients in the current study and the documented extrahippocampal damage in others, the current results leave open the question as to whether the observed impairment in semantic future thought is attributable specifically to hippocampal damage or could be due to the damage to other MTL regions. The evidence favoring a hippocampal locus for the deficit comes from the finding in the current study that a patient with volumetrically documented damage limited to the hippocampus performed similarly to the amnesic group as a whole. On the other hand, recent observations of activity not only in the hippocampus but also in the parahippocampal gyrus during a semantic future-thinking task (Abraham et al., 2008), as well as findings of perirhinal involvement in semantic memory (Davies et al., 2004), suggest that extrahippocampal regions may also contribute to semantic future thought. Future studies will be needed to clarify more precisely which MTL regions are essential for semantic prospection.

The finding that MTL processes are critical for constructing rich mental simulations of the semantic future and past has implications for understanding prior observations of preserved episodic prospection in MTL amnesia. It has been argued that such preservation may reflect the ability of patients to draw on preserved semantic memory stores. The current findings of impaired semantic memory and future thought in MTL amnesia provide constraints on this interpretation, insofar as instances of preserved episodic prospection following MTL lesions cannot be due to the generation of the kind of detailed semantic elaborations of the past that were probed in this study. Our findings leave open the possibility, however, that episodic prospection in amnesia can be supported by access to preserved scripts in semantic memory that are well rehearsed or routinized (Maguire et al., 2010; Cooper et al., 2011; Maguire and Hassabis, 2011). Such generic information may appear rich and multifaceted and may appear to be novel; however, retrieval of such information may not place high demands on hippocampal processes supporting generative retrieval or binding. Indeed, it is known that information that has become overlearned or routinized can be retrieved independently of the MTL (Steinvorth et al., 2005; Leyhe et al., 2010). In this context, a direct comparison of elaborated retrieval of generic versus singular semantic knowledge in amnesia will be theoretically compelling.

In conclusion, we demonstrated for the first time that amnesic patients' impairment in future thinking is not limited to episodic prospection but extends to semantic prospection. Our results suggest that the MTL plays a critical role in the creation of elaborate semantic simulations of both the future and the past and provide novel evidence from MTL amnesia that memory and prospection are linked in the semantic domain. An important area for future research will be to determine the specific nature of the MTL processes and the regions that support semantic prospection.

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