Published in final edited form as:

Neuropsychologia. 2015 December ; 79(0 0): 42–52. doi:10.1016/j.neuropsychologia.2015.10.017.

Remote semantic memory is impoverished in hippocampal amnesia

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Abstract

The necessity of the hippocampus for acquiring new semantic concepts is a topic of considerable debate. However, it is generally accepted that any role the hippocampus plays in semantic memory is time limited and that previously acquired information becomes independent of the hippocampus over time. This view, along with intact naming and word-definition matching performance in amnesia, has led to the notion that remote semantic memory is intact in patients with hippocampal amnesia. Motivated by perspectives of word learning as a protracted process where additional features and senses of a word are added over time, and by recent discoveries about the time course of hippocampal contributions to on-line relational processing, reconsolidation, and the flexible integration of information, we revisit the notion that remote semantic memory is intact in amnesia. Using measures of semantic richness and vocabulary depth from psycholinguistics and first and second language-learning studies, we examined how much information is associated with previously acquired, highly familiar words in a group of patients with bilateral hippocampal damage and amnesia. Relative to healthy demographically matched comparison participants and a group of brain-damaged comparison participants, the patients with hippocampal amnesia performed significantly worse on both productive and receptive measures of vocabulary depth and semantic richness. These findings suggest that remote semantic memory is impoverished in patients with hippocampal amnesia and that the hippocampus may play a role in the maintenance and updating of semantic memory beyond its initial acquisition.

Keywords

semantic memory; semantic richness; hippocampus; consolidation; remote memory

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1. Introduction

Semantic memory refers to knowledge of vocabulary, facts and concepts about the world, and general information about oneself (Tulving, 1972). The role of the hippocampus in its support of semantic memory has been a topic of considerable debate. According to one view, the hippocampus is necessary for the acquisition of new semantic knowledge, providing the relational binding of the arbitrarily related phonological, conceptual, and orthographic components of word knowledge and the arbitrarily related pieces of content that make up a semantic fact about the world or ourselves (e.g., Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2001; Gabrieli et al., 1988; Manns et al., 2003; Postle and Corkin, 1998; Warren and Duff, 2014). A second view holds that the hippocampus may not be necessary for the acquisition of semantic information and that other medial and/or lateral temporal lobe structures can accomplish, at least some aspects of this type of learning, on some occasions, in the absence of normal hippocampal functioning (e.g., Vargha-Khadem et al., 1997; O’Kane et al., 2004; Sharon et al., 2011; Tulving et al., 1991).

While these two views differ regarding the role and nature of the hippocampus in acquiring new semantic memory, there has been more general consensus that remote semantic memory, acquired long in advance of any pathology, and outside the window of any retrograde amnesia or temporal gradient effects, is intact following hippocampal and more widespread MTL damage (e.g., Winocur and Moscovitch, 2011). With respect to vocabulary, patients with hippocampal amnesia perform within normal limits on neuropsychological measures of vocabulary knowledge and naming, and do not have aphasia or semantic dementia (Kensinger et al., 2001). In experimental tasks examining remote word knowledge (e.g., when asked to name items, or match a label with a short phrase, definition, or sentence explaining its meaning) patients with hippocampal pathology do not differ significantly from healthy comparison participants (Gabrieli et al., 1988; Verfaellie et al., 2000; Manns et al., 2003). The notion that remote semantic memory is intact in amnesia has fit well with the view that over time, semantic information becomes independent of the hippocampus through neocortical consolidation (e.g. McClelland et al., 1995; O’Reilly and Rudy, 2000) and that the storage, processing, and use of semantic information are also hippocampally independent, depending more on anterior and lateral temporal lobes (Tranel et al., 1997; Binder et al., 2009; Schmolck et al., 2002; Smith and Squire, 2009).

Beyond the acquisition phase, the hippocampus and its associated processes may also support the retrieval and use of previously acquired semantic memory. Neuroimaging studies point to hippocampal involvement during retrieval of semantic memory in healthy individuals (e.g., Burianova and Grady, 2007; Burianova, McIntosh, and Grady, 2010; Ryan, et al., 2008; Ryan, et al., 2010; Whitney et al., 2009; Sheldon and Moscovitch, 2012) and studies in amnesia have reported deficits in the flexible and rich use of semantic information during communication (Race et al., 2013; Verfaellie et al., 2014). Some authors have also linked deficits in semantic memory retrieval to impaired episodic memory (Sheldon et al., 2013; Greenberg et al., 2009). Despite these links in the literature between hippocampus and semantic memory beyond the acquisition phase the broader consensus has remained that remote semantic memory in amnesia is intact.

In the current study, we revisit the notion that remote semantic memory is intact in amnesia and independent of the hippocampus by examining the depth of vocabulary knowledge in patients with hippocampal amnesia. In addition to the work mentioned above, the specific motivation for this study comes from consideration of perspectives on word knowledge and learning from the psycholinguistic and second language acquisition literatures, and recent discoveries about the time course of hippocampal contributions to on-line processing and reconsolidation. Bringing together these perspectives and findings, we predict deficits in remote semantic memory in amnesia. Two primary observations lead to this prediction.

The first observation relates to depth of word knowledge, the amount of information associated with a word or concept. Studies of semantic knowledge in hippocampal amnesia have examined associative knowledge of famous people including tests requiring participants to pick out famous names from foils or match famous faces with their names (e.g., Westmacott and Moscovitch, 2002; Reed and Squire, 1998). This work supports the view that the hippocampus plays a time-limited role in supporting semantic memory, with amnesic patients performing similarly to healthy comparison participants. Most studies of semantic memory in amnesia, however, have focused on surface-level pairings of vocabulary or lexical information. Across studies, participants might be shown a picture of a lemon and asked to name it, asked to identify whether L-E-M-O-N or L-E-N-A-K are real words, or asked to match the label 'lemon' to a short definition (e.g. a yellow citrus fruit). The fact that patients with hippocampal amnesia do not differ from healthy comparison participants on these types of tasks has been taken as evidence that their remote semantic memory is intact.

In other literatures, what it means to know a word extends beyond surface-level pairings to include how much information is associated with a word or concept, how words are used, and how they co-occur with other words in language use (Read 1993; 1998). Returning to the example of 'lemon', under the umbrella term of semantic richness (defined as the amount of semantic information associated with a word or concept; Pexman et al., 2002), measures of depth of knowledge include the number of features of a word or concept (e.g., tastes sour, native to Asia, grows on small evergreen trees, eaten in pies, used in tea) (Pexman et al., 2002; Yap, 2011), the number of different senses a word can take (e.g., the fruit, the tree, the color, the scent, a defective automobile) (Taler et al., 2013), and the number of word associates or collocates of the concept (e.g., lime, juice, zest, marmalade, rind, wedge, sole, sour) (Laszlo and Federmeier, 2011). While vocabulary breadth (the number of words one knows) and surface-level pairing information may not differ significantly between patients with amnesia and healthy comparison participants, less is known about vocabulary depth of remotely acquired words in amnesia.

The second observation relates to the time course over which a word is learned. In studies of word learning with patients with hippocampal amnesia, participants either fail or succeed in reaching criterion of a surface-level pairing within several trials or sessions seldom stretching more than a day or two (e.g., Gabrieli et al., 1988; Duff et al., 2006). Yet, various literatures on word learning suggests that the learning process is more protracted, spanning days, weeks, and even years (Carey, 2010; McMurray et al., 2012). Over time, and with extensive experience with a word or concept, people associate more and more information

with each concept (McGregor et al., 2002). That is, the number of features and senses associated with a word grows over time as the learner acquires more information about the varied ways the word or concept can be used across a multitude of situations.

If word learning is a protracted process, one that is possibly never fully complete, then the hippocampus may support “remote” knowledge by strengthening and creating new connections among and between words and adding new features or senses to existing representations. From the perspective that the hippocampus does support word learning, and the updating of relational representations more broadly (e.g., Eichenbaum and Cohen, 2001), the hippocampus could be involved in adding new features, senses, and other information about a word or concept over time with preexisting information. This perspective would fit with recent work showing that the hippocampus contributes to the updating and maintenance of relational information in the moment (Hannula et al., 2006; Warren et al., 2011) and to the updating and strengthening of previously acquired information through reconsolidation (McKenzie and Eichenbaum, 2011; Lee, 2008).

Using measures of semantic richness, we revisit the notion that remote semantic memory is intact in amnesia and independent of the hippocampus by examining vocabulary depth of remotely acquired words in patients with hippocampal amnesia. We predict that patients with bilateral hippocampal damage will display impoverished semantic memory, performing worse on a receptive measure of vocabulary depth and richness and will produce fewer features and senses for target words than a group of demographically matched healthy comparison participants and a group of brain damaged comparison participants. Such a finding would go beyond previous reports that the hippocampus supports the processes associated with retrieving and using semantic memory to also suggest that hippocampus may play a protracted and sustained role in the life-long development and maintenance of semantic knowledge by establishing new relations within and across items in the semantic memory system.

2. Methods

2.1 Participants

Participants were five (one female) patients with bilateral hippocampal damage and severe declarative memory impairment (HC group), five (four female) brain damaged comparison participants with damage outside the medial temporal lobe and no declarative memory impairment (BDC group), and 24 healthy comparison participants free of neurological and psychiatric disease (NC group), matched to the HC and BDC participants on sex, age, and level of education. The patients were recruited from the Patient Registry of the University of Iowa’s Division of Behavioral Neurology and Cognitive Neuroscience and were characterized neuropsychologically and neuroanatomically according to established protocols in our laboratory (Frank et al., 1997; Tranel, 2007). All patients in the HC and BDC groups have stable, non-progressive lesions. The Institutional Review Board approved all procedures for Human Subjects Research at the University of Iowa.

For the HC group, etiologies included anoxia/hypoxia (1846, 2363, 2563), resulting in bilateral hippocampal damage, and herpes simplex encephalitis (HSE) (1951, 2308),

resulting in more extensive bilateral medial temporal lobe damage affecting the hippocampus, amygdala, and surrounding cortices (see Figure 1). Structural MRI examinations completed on 4 of the 5 patients confirmed bilateral hippocampal damage, and volumetric analyses performed on 3 of the 5 patients revealed significantly reduced hippocampal volumes (studentized residual differences in hippocampal volume relative to a matched comparison group down by at least 2.6 z-scores; Allen et al., 2006). For Participant 2563 (who wears a pacemaker and was unable to undergo MRI examination), anatomical analysis was based on computerized tomography, and damage confined to the hippocampal region was visible. For the three anoxic patients, there is no damage to the lateral temporal lobes or to the anterior temporal poles. For patient 1846, more in-depth neuroanatomical analyses were available and other medial temporal lobe structures were judged to be within the normal range through volumetric analyses (Warren et al., 2012).

Performance on tests of neuropsychological functioning revealed a severe and selective impairment in declarative memory ($M=59$; Wechsler Memory Scale–III General Memory Index) while performance across other cognitive domains including measures of verbal IQ, vocabulary and semantic knowledge was within normal limits (Table 1). This intact performance on tests of naming and semantic information, together with their lack of aphasia or anomia, suggests that lexical and semantic access is within normal limits as measured by standard neuropsychological testing. There was also no evidence of the category-specific semantic deficits associated with semantic dementia (e.g., disproportionate deficit for living things (Lambon Ralph et al., 2007) or for significant deterioration of semantic knowledge over time (i.e., we have studied some of these patients for 20 years and the language abilities of all these patients extensively over the decade, see Duff and Brown-Schmidt, 2012).

We employed a BDC group to differentiate deficits due to hippocampal damage specifically from any deficits due to brain damage more generally. BDC participants included 5 patients with bilateral damage to the ventromedial prefrontal cortex (Supplementary figure 1) secondary to tumor resection ($n=3$), stroke ($n=1$), and sub-arachnoid hemorrhage ($n=1$). Critically, with the exception of a significant difference between the BDC and HC group on Wechsler Memory Scale General Memory Index ($t = -7.72$, $p < 0.001$), there were no group differences on other neuropsychological measures from the Wechsler Adult Intelligence Scale including Verbal IQ ($p > 0.07$), Vocabulary ($p > 0.40$), and Information ($p > 0.39$) or on the Boston Naming Test ($p > 0.10$), and Controlled Oral Word Association ($p > 0.06$) (Table 1).

Non-brain damaged healthy comparison participants (NC) included 24 individuals free of neurological and psychiatric disease, case matched to the amnesic and BDC participants on sex, age, and level of education (One to two NCs were matched to each amnesic and BDC participants). One-way ANOVAs reveal no significant group differences between HC, BDC, and NC groups for age ($p > 0.07$) or education ($p > 0.23$).

2.2 Experimental Procedures

2.2.1 Word Associates Test—The Word Associates Test or WAT (Read, 1993; 1998) is a widely used measure of depth of vocabulary knowledge (e.g. Greidanus, et al., 2006; Qian,

2002; Qian and Schedl, 2004). A paper and pencil version of the 1998 form of the WAT, available at <http://www.lex tutor.ca/>, was given to participants. Instructions were read and two example problems were provided. The instructions and examples were kept in view on the table during testing. The test contains 40 questions assessing knowledge of potential synonyms and collocates (words that often follow the target in a phrase or sentence) of given target words. Each question has a target adjective in bold (e.g., sudden), below which are eight possible associates, 4 possible synonyms to the target (e.g., beautiful, quick, surprising, thirsty), and 4 possible collocates (change, doctor, noise, school). Participants were instructed to select 4 matching associates out of the 8 possibilities by placing an X next to each intended answer. (Correct responses for the example above would be quick and surprising for synonyms and change and noise for collocates.) Each correct response was scored for a total of 160 possible points. Points were not deducted for incorrect responses.

2.2.2 Familiarity Survey for Features and Senses Tasks—Before completing the features and senses tasks (described below), participants first rated their familiarity with the words on a scale from 1 (not at all familiar) to 9 (extremely familiar). The instructions (Please circle the number that best reflects how familiar you are with the thing to which the word refers. Remember: 1 = Not at all familiar, 5 = Familiar, 9 = Extremely familiar) were repeated at the top of each page.

2.2.3 Features Task—Thirty-five words (See supplementary Table 1) were chosen from a set of feature production norms (McRae et al., 2005). Instructions and examples were left in front of participants and were repeated by the experimenter regularly. The experimenter read each target word aloud. Participants were given 2 minutes per word to verbally list as many features as possible. If participants stopped responding or indicated they could not think of any more features, the target word was repeated, they were encouraged to keep trying, and were asked to think of other features for the target. Responses were video recorded for later transcription and analysis.

2.2.3.1 Transcription and Coding of Features Data: Feature responses were transcribed and coded by the first author and a research assistant, who was blind to participant status and study hypotheses. Participant responses were transcribed orthographically and the two transcribers reached consensus on the accuracy and completeness of the transcripts. Coding of the features was done from these transcripts. Methods used to divide and code features closely followed those used by McRae and colleagues (McRae et al., 2005). Responses were coded as features or non-features. Responses containing multiple features were broken up into their smallest constituent features (e.g. for target shirt: “Can be a pullover or a button down,” is coded as two features: 1) Can be a pullover, 2) Can be a button down). Responses coded as non-features were further characterized as repetitions of previous responses, subjective evaluations (Strawberry: “I like strawberries.”), personal anecdotes (Colander: “My mother had one.”), factually incorrect (Dolphin: “An amphibian.”), or as unrelated facts (Nightingale: “Some birds quack and some birds gobble.”). Personal anecdotes were not coded as features, but if the anecdote included semantic features of the target word, these were extracted and coded (For target garage: “I never parked my car in the garage, I parked outside.” The feature place to park car was extracted).

2.2.4 Senses Task—Forty-one words (Supplementary Table 2) were chosen from normed databases (Nelson et al., 1980; Twilley et al., 1994). Participants were instructed that some words can have different senses with slightly different meanings, given two examples (e.g., the word “bank” can mean a financial institution, or the bank of a river), and asked to list as many senses as possible for each target word. Instructions and examples were left on the table in front of participants for the duration of the task and were repeated by the experimenter regularly. The experimenter read each word aloud. Participants were given 1 minute to state as many senses as possible. If participants indicated they couldn’t think of more senses, they were encouraged to keep trying. Responses were video recorded for later transcription and analysis.

2.2.4.1 Transcription and Coding of Senses Data: The first author and a research assistant blind to participant status and study hypothesis transcribed the responses. Participant responses were transcribed orthographically and the two transcribers reached consensus on the accuracy and completeness of the transcripts. Coding of the senses was done from these transcripts. Responses were first evaluated in accordance with WordNet (Miller, 2010) the normative database from which many previous psycholinguistic research studies on word senses have drawn. Responses included in WordNet were coded as a correct sense of the target word. Because target words were read aloud to participants and were not presented visually, some responses included homophones to the target word (e.g. fare: transportation cost vs. fair: impartial). Senses of homophones were coded as a correct sense of the target word. Because Wordnet does not include seemingly obvious senses of some target words (for can there are no entries for possibility, or is able to), responses not included as one of the accepted senses in WordNet were evaluated with definitions from the Merriam Webster Dictionary (merriam-webster.com/dictionary) with responses matching one of the definitions coded as a correct sense of the target word. Responses indicating a proper noun that did not appear in WordNet were also accepted as correct senses of the target words. Any other responses were excluded from analysis.

3. Results

3.1 Word Associates Test

On the Word Associates Test (Figure 2), a one-way ANOVA showed a statistically significant difference between groups ($F_{(2, 31)} = 33.85$, $p < .001$, $\eta^2_G = 0.69$). Planned comparisons using the Holm procedure for multiple comparison revealed that the HC group ($M = 123.6$, $SD = 7.3$) performed significantly worse on the WAT than the BDC group ($M = 145.4$, $SD = 6.5$, $p < .001$), and the NC group ($M = 146.8$, $SD = 5.3$, $p < .001$), while BDCs did not differ from NCs ($p > 0.6$). This pattern held for the two sub-scales of the WAT (Synonyms: $F_{(2,31)} = 7.56$, $p < 0.005$, $\eta^2_G = 0.33$ and Collocates: $F_{(2,31)} = 30.10$, $p < .001$, $\eta^2_G = 0.66$), with the comparison groups performing indistinguishably from each other (Synonyms: $p > 0.69$. Collocates: $p > 0.75$), and both performing significantly better than the HC group for synonyms (BDCs: $p < 0.05$. NCs: $p < 0.005$) and collocates (BDCs: $p < .001$. NCs: $p < .001$). Critically, this deficit in the HC group was observed in the absence of having to generate a response and when all the correct information was visible in front of the participants.

3.2 Familiarity Ratings

Familiarity ratings for words in the features and senses tasks did not differ between groups (Features: $F_{(2, 31)} = 3.01$, $p > 0.06$. Senses: $F_{(2, 31)} = 1.62$, $p > 0.21$). All groups had a mean familiarity rating of 8.4 or greater (out of 9) for both tasks, indicating that these words were subjectively (and equally) well known and familiar to all participants.

3.3 Features Task

On the features task, Welch's F test was used because the homogeneity of variance assumption of the Levene test was not met ($p < 0.05$). A one-way ANOVA showed a statistically significant difference between groups (Welch's $F_{(2, 11.4)} = 27.8$, $p < .001$, $\eta^2_G = 0.38$). Planned comparisons using the Holm procedure for multiple comparisons revealed that the HC group ($M = 9.92$, $SD = 2.9$) performed significantly worse than both BDCs ($M = 20.20$, $SD = 1.3$, $p < 0.02$) and NCs ($M = 22.25$, $SD = 6.5$, $p < 0.001$), while there was no difference between BDC and NC groups ($p > 0.47$).

Looking closer at the data, we found no significant group differences for the number of non-features produced per target ($p > 0.21$), the number of repetitions ($p > 0.20$), the number of subjective evaluations ($p > 0.46$), the number of personal anecdotes ($p > 0.09$), the number of unrelated responses ($p > 0.27$), or the number of factually incorrect responses ($p > 0.62$). Thus, the deficit in the HC group was limited to the total number of features they could associate with the target word.

A representative example of responses is shown in Table 2 for two participants with hippocampal amnesia (1951 and 2363), a BDC participant, and a healthy comparison participant to the target word 'menu'. Whereas the healthy comparison participant was able to produce 24 features for the word 'menu', and the BDC produced 25, the two amnesic participants were able to produce 8 and 6 features, respectively.

Consistent with our assessment that these patients do not have semantic dementia or category specific deficits, there was proportional impairment in the features task for both living and non-living targets. The HC group produced an average of 10.23 features for living target words and 9.93 features for non-living targets a difference that was not statistically significant ($t = 0.162$, $p = .88$). This was true for the anoxic ($t = 0.09$, $p = .93$) and the HSE subgroup ($t = 0.14$, $p = .90$).

3.4 Senses Task

On the senses task, Welch's F test was used because the homogeneity of variance assumption of the Levene test was not met ($p < 0.05$). A one-way ANOVA showed a statistically significant difference between groups (Welch's $F_{(2, 12.5)} = 33.4$, $p < .001$, $\eta^2_G = 0.40$). Planned comparisons using the Holm procedure for multiple comparisons revealed that the HC group ($M = 2.49$, $SD = 0.19$) produced significantly fewer senses on average than the BDC group ($M = 3.29$, $SD = 0.21$, $p < 0.04$), and the NC group ($M = 3.61$, $SD = 0.58$, $p < 0.001$), but the BDCs did not differ from NCs ($p > 0.21$).

As Figure 4 displays, HC participants produced significantly fewer senses per target than comparison participants. A representative example of responses is shown in Table 3 for 2 participants with hippocampal amnesia and 3 comparison participants.

3.5 Further consideration of the data

These results show striking deficits across three tasks in the HC group on both productive and receptive measures. Here, we further examine these data and consider possible explanations for the observed deficits.

As reported above, the familiarity ratings for words in the features and senses tasks did not differ between groups. To ensure that inclusion of individual unfamiliar words did not affect the results here, or disproportionately disadvantage the participants with amnesia, we reexamined the data to include only those words judged to be highly familiar by participants. Removing words judged to be unfamiliar (familiarity < 5 out of 9) from the full data set did not change the results. We still observed significant differences between groups for both the Features task (Welch's $F_{(2, 11.6)} = 26.5$, $p < .001$) and the Senses task (Welch's $F_{(2, 12.8)} = 34.4$, $p < .001$), with the HC group performing significantly worse than the both comparison groups (Features: HC $M = 10.06$, BDC $M = 20.41$, $p < 0.02$. NC $M = 22.16$, $p < 0.001$; Senses: HC $M = 2.51$. BDC $M = 3.28$, $p < 0.05$. NC $M = 3.62$, $p < 0.005$), but the comparison groups did not differ from each other (Features: $p > 0.05$. Senses: $p > 0.18$).

Although verbal fluency and generation ability, as measured by the COWA, did not differ between the HC and BDC participants at the group level ($t = -2.14$, $p > 0.065$), two of the amnesic participants (1846 and 2308) scored below population norms. Deficits in verbal fluency have also been reported in other patients with hippocampal pathology (Sheldon, Romero, and Moscovitch, 2013). However, differential generative abilities alone do not appear to explain the results. First and foremost, disruptions in fluency or generative abilities cannot account for the HC group's significantly worse performance on the WAT, a receptive measure of vocabulary depth that does not require generative abilities from participants, but rather provides all the information needed to complete the test in front of the participant. WAT performance correlates strongly with performance on the features task ($r(32) = 0.51$, $p < 0.01$) and the senses task ($r(32) = 0.53$, $p < 0.001$) across participants. Next, consider data from HC and BDC patients who performed similarly on COWA. HC patient 1951 and BDC 3350 both scored 40 on COWA, yet while 3350 produced an average of 22.15 features per target word, 1951 produced only 10.8 features, on average. Similarly, HC 2563 scored 37 on COWA while BDC 2352 scored 34. Yet for features (2352 = 19.74 features per target word; 2563 = 12.34) large differences are seen for performance despite highly similar COWA scores. If data from the two amnesic patients with low COWA scores are excluded, for the features task, the remaining 3 patients with COWA scores in the normal range still perform significantly worse ($M = 11.52$) than the 24 healthy comparisons ($M = 22.25$, $p = 0.017$). Finally, the data from the HC and BDC groups were reanalyzed using COWA performance as a covariate, and the same pattern of results were observed. Specifically, for the features task, a one-way ANOVA showed a statistically significant difference between groups ($F_{(1, 8)} = 8.45$, $p < .02$, $\eta^2_G = 0.51$). Planned comparisons revealed that the HC group (adjusted $M = 12.43$) produced significantly fewer features than the BDC group (adj. $M = 17.75$, $p <$

0.0001). This was true for the senses task ($F_{(1, 8)} = 7.35$, $p < .05$, $\eta^2_G = 0.48$. HC adj. $M = 2.69$. BDC adj. $M = 3.10$, $p < 0.01$) and the WAT ($F_{(1, 8)} = 5.57$, $p < .05$, $\eta^2_G = 0.41$. HC adj. $M = 127.85$. BDC adj. $M = 141.15$, $p < 0.01$). Thus, these additional analyses suggest that the findings reported cannot be simply accounted for by a disruption in verbal fluency or generation in two of the amnesic participants.

Is it possible that impairments in episodic memory could explain the patients' impoverished semantic memory on these tasks? That is, are participants drawing on specific episodes in memory to access semantic knowledge (e.g., thinking of sitting on a river bank to have lunch with a friend last week to generate different senses of the word 'bank') or can participants draw on more decontextualized knowledge of the items (e.g., the extracted sum of knowledge that is not longer linked to any given specific episodes)? While we cannot definitively rule out a contribution of episodic memory to task performance, we do not believe that episodic memory deficits are driving the pattern of results observed here. One potential source of evidence for this comes from the features task where some participants responded to target words with a personal anecdote. One example of such a personal anecdote comes from patient 1951 who, to the target word mug, responded "I remember going to a root beer stand in Michigan where you could pay 25 or 50 cents for a giant mug of root beer." The number of these personal anecdotes did not differ statistically across groups ($F_{(2, 31)} = 2.58$, $p > 0.09$). The HC group produced 0.25 anecdotes per target word on average, while NCs produced 0.13 and BDCs 0.38. This suggests that comparison participants were not leveraging personal (past or possibly future) episodic memory at a greater rate than amnesic patients, as captured by this measure and there was no obvious advantage in performance for the BDC group who produced more personal anecdotes than the NC group. Furthermore, any episodic memory deficits are unlikely to explain the amnesic participants' deficits on the WAT, a receptive measure of vocabulary depth where all correct answers are on the page in front of participants. While it is possible that a participant could produce an episodic memory while making these judgments (e.g., recalling a sudden noise during an explosion when judging if sudden and noise are collocates), a simpler strategy given the task demands (to determine if the two words co-occur in written or spoken language) might be to conduct truth-value judgments or grammaticality judgments typical in the language literature and that do not require episodic memory. While we cannot definitively rule out any contributions made by episodic memory to these tasks, the large effect sizes seen across all three tasks suggest that even a small contribution could not explain the large and consistent group differences. That said, future studies could attempt to disentangle these issues by having conditions that explicitly ask participants to leverage episodic memory to complete the tasks and determine if such manipulations improve performance.

Finally, there is variability in the extent of MTL damage in the HC group with two participants who have extensive MTL damage due to HSE and three anoxic participants with more limited MTL damage. Comparing the performance of these two subgroups, we find the two groups do not differ on WAT performance (anoxic $M = 121.0$, $SD = 5.00$; HSE $M = 127.5$, $SD = 10.61$, $t = -0.81$, $p < 0.54$) and both subgroups performed much worse than NCs ($M = 147.0$). This pattern held for features (anoxic $M = 11.38$, $SD = 0.98$; HSE $M = 7.87$, $SD = 4.14$, $t = 1.18$, $p < 0.44$; NC $M = 20.42$), and senses (anoxic $M = 2.56$, $SD = 0.17$. HSE

$M = 2.39$, $SD = 0.24$, $t = -0.81$, $p < 0.50$; $NC M = 3.56$). That said, while anoxia can affect the hippocampus disproportionately, it may not do so selectively and the lack of anatomical measurement on extra-hippocampal structures is a limitation of the current study. To further explore this issue, we turn to patient 1846. Analyses of lobar gray- and white-matter volumes for this patient reveal studentized residual volumes to be within the normal range when accounting for age and sex, in the cerebrum overall, and in the frontal, parietal, and temporal lobes specifically (Allen et al., 2006). Patient 1846 has significant hippocampal volume loss (Figure 1; Table 1) but other medial temporal lobe structures were judged to be within the normal range through additional volumetric analyses (Warren et al., 2012). The Crawford-Howell t-test for case-control comparisons shows that 1846 performed significantly worse than comparisons across the 3 tasks. Specifically, 1846 ($M = 10.38$) performed worse than both comparison groups on features ($NC M = 22.25$, $t = -1.79$, $p < 0.05$. $BDC M = 20.20$, $t = -6.65$, $p < 0.01$), senses (1846 $M = 2.366$, $NC M = 3.61$, $t = -2.11$, $p < 0.05$. $BDC M = 3.29$, $t = -4.10$, $p < 0.01$), and WAT performance (1846 = 116, $NC M = 146.8$, $t = -5.68$, $p < 0.001$. $BDC M = 145.4$, $t = -4.10$, $p < 0.01$). The Crawford-Howell t-test reveals no difference between this participant's performance and those of the two HSE patients with known extra-hippocampal MTL damage on features (HSE $M = 7.87$, $t = 0.49$, $p < 0.71$), senses (HSE $M = 2.391$, $t = -0.08$, $p < 0.95$), or WAT performance (1846 = 116, HSE $M = 127.5$, $t = -0.88$, $p < 0.54$). Indeed, as can be seen in Figures 2 – 4, despite having documented damage limited to the hippocampus bilaterally, and having much smaller lesions than the HSE patients, patient 1846's scores are among the lowest 2 across all participants and across all 3 tasks. That the patients all perform so consistently below comparisons, and so similarly to each other, suggests that the differences in anatomy are not driving the results, but rather that their shared hippocampal damage, together with the purported functions of the hippocampus, provide the most parsimonious account of the large deficits seen here.

4. Discussion

Remote semantic memory has long been considered independent of the hippocampus and intact in hippocampal amnesia. Indeed, hippocampal amnesia does not result in the type of catastrophic disruptions in semantic memory that can be observed as a consequence of semantic dementia, and patients with hippocampal amnesia do not differ from healthy comparison participants on standardized naming tasks or simple definition-matching tasks. However, when more sensitive measures of semantic memory are used, those examining the depth and richness of semantic knowledge, we find that participants with hippocampal amnesia perform significantly worse than healthy and brain-damaged comparison participants. This deficit is observed across both productive and receptive tasks and for words rated as highly familiar. These findings suggest that the hippocampus may play a role in semantic memory beyond its initial acquisition, and beyond the processes associated with retrieving and using such knowledge.

The observed deficits in word knowledge reported here suggest that remote semantic memory in hippocampal amnesia is impoverished. The hallmark processing features of the hippocampus including its capacity for relational binding (Cohen and Eichenbaum, 1993; Eichenbaum and Cohen, 2001), reconsolidation (McKenzie and Eichenbaum, 2011; Lee,

2008) and flexible integration of information (Zeithamova and Preston, 2010), situate it well to meet the demands of maintaining, updating, and using semantic memory across experiences and over time (also see Duff and Brown-Schmidt, 2012). Indeed, various treatments of word knowledge and learning suggest that word knowledge includes how much information is associated with a word or concept (e.g., McGregor et al., 2002; Laszlo and Federmeier 2011) and that the process of learning these associations is protracted over time (Carey, 2010; McMurray et al., 2012). From this perspective, the hippocampus may support remote semantic knowledge by strengthening and enriching existing semantic representations through the addition and integration of new information (e.g., features or senses of a word) as words are retrieved and used in novel contexts in the negotiation of meaning in the moment. Whether previously acquired semantic representations become impoverished in amnesia due to a failure to update and enrich knowledge, a failure to maintain and strengthen existing knowledge, or some combination of processes is an open question and ripe for future discussion and study.

The findings here add to a large body of work on the role of the hippocampus in semantic memory. Most of this work has focused on the initial acquisition of new semantic information where patients with hippocampal amnesia are asked to learn new associations rather than add to or update existing representations (e.g., Hayman et al., 1993; Verfaellie, et al., 2000; Bayley and Squire, 2002; Schmolck, et al., 2002; O’Kane, et al., 2004; Stark, et al., 2005; Manns et al., 2003; Gabrieli et al., 1988; Duff et al., 2006; Warren and Duff, 2014; Vargha-Khadem et al., 1997; Sharon et al., 2011). The overwhelming majority of these studies report profound deficits in acquiring new semantic information, and even when some new semantic learning is documented, that learning is described as slow, sparse, and inflexible (e.g., O’Kane et al., 2004; Bayley and Squire, 2002). Related to the current findings, Skotko and colleagues (2004) reported a benefit (albeit temporary) in learning semantic information in H.M. when new information could be anchored or added to existing information or schemas (Skotko, et al., 2004). The general idea being that it is easier to build or add to an existing representation than it is to create a brand new association and that such processes are possible (although not normal) in the absence of a functioning hippocampus. The proposed mechanisms for such slow, gradual learning in amnesia include intact neocortical learning processes (McClelland et al., 1995; O’Reilly and Rudy, 2000). More recent accounts of neocortical learning, however, suggest that new associations can be rapidly incorporated into neocortical structures if they are consistent with prior knowledge (Tse et al., 2007; 2011; McClelland, 2013). That is, neocortical learning may not be as much about slow or gradual learning as it is prior knowledge dependent (McClelland, 2013). However, this process may not be completely independent of the hippocampus. For example, although HM was able to learn some new semantic information for which he already had some existing knowledge, he learned remarkably little and not at a normal rate (Skotko et al., 2004; also see MacKay et al., 1998 for discussion of semantic production deficits in HM). Furthermore, word learning procedures like fast mapping, thought to rapidly integrate new semantic information into cortical memory networks through retrieval of a related known concept (Coutanche and Thompson-Schill, 2014), fail to produce durable learning in patients with hippocampal damage (Smith et al., 2014; Warren and Duff, 2014, although see Sharon et al., 2011). In the animal literature, Tse and colleagues (2007) found

that removing the hippocampus after successful learning of schema-consistent information prevented the learning of additional associations. These results, and the findings presented here, suggest that, in addition to initial learning of semantic representations, the hippocampus may also contribute to the addition of new information to existing neocortical knowledge networks. The nature and time course of the interactions between hippocampus and neocortex in initial and extended learning and maintenance of semantic information, as well as the role of consistency, will be important avenues for future studies (see McClelland, 2013 for further discussion).

While the current study is the first to our knowledge to report impoverished remote word knowledge in amnesia, these results fit neatly with recent studies reporting that other aspects of semantic memory use are impoverished in amnesia. Rosenbaum et al. (2004) examined autobiographical memory in patient K.C. and found that, in addition to deficits in autobiographical episodic information, K.C. also displayed impairments on the personal semantic schedule of the Autobiographical Memory Interview (Koppelman et al., 1989). Sheldon and colleagues (2013) asked patients with medial temporal lobe amnesia to freely associate as many words as possible that were related to a cue word. The authors reported that the patients with amnesia provided significantly fewer words than healthy comparison participants. The authors suggested that comparison participants, unlike the patients with amnesia, were able to leverage intact episodic memory in producing the associated words (Sheldon et al., 2013). Another explanation for those data are that the patients simply had less information associated with the cue words.

Other studies have examined how the hippocampus supports the rich use of semantic knowledge. Race and colleagues (2013) examined semantic prospection by asking patients with medial temporal lobe amnesia to imagine future issues occurring in the public domain. Patients with amnesia could list general future semantic facts but, when probed to elaborate, produced impoverished descriptions that lacked semantic detail, suggesting that the hippocampus plays a critical role in the construction of detailed semantic simulations (Race et al., 2013). This same group found a similar deficit when investigating well-known semantic narratives (e.g., fairy tales) (Verfaellie et al., 2014). A previous study (Rosenbaum et al., 2009) found the same deficit, fewer semantic details when recalling well-known fairy tales and bible stories. Although the amnesic patient was normal on recognition tests of these details, using that knowledge flexibly and richly when recalling the stories was found deficient.

Studies of semantic memory in amnesia are often used to provide evidence for or against the idea that semantic memory and episodic memory are equally dependent on the functionality of the hippocampus. The current study, and those described above pointing to impoverished semantic memory across a range of tasks, provides additional evidence that, like episodic memory, semantic memory depends critically on the hippocampus. Indeed, just as hippocampal pathology has been shown to have deleterious effects on episodic memory for both the remote past and the future (Hassabis et al., 2007; Kurczek et al., 2015; Nadel and Moscovitch, 1997; Moscovitch, et al., 2005; Race et al., 2011; St-Laurent et al., 2014) hippocampal damage also disrupts semantic memory across time. Thus, the same hallmark processing features of hippocampus (e.g., relational binding, representational flexibility,

reconsolidation, flexible integration and (re)combination of information) that support episodic memory, simulation, and other creative and (re)constructive processes (and that when disrupted produce deficits across these abilities) also appear to support maintaining, updating, and using semantic memory across experiences and over time. It should be noted that other studies have suggested that episodic memory may contribute to performance on semantic memory tasks (i.e. Greenberg et al., 2009; Ryan et al., 2008). We agree with those who have commented on the difficulty in parsing the contributions that episodic and semantic memory play in a given task (Tulving, 2005; Ryan et al., 2008; Greenberg et al., 2009) and suggest that future work that attempts to manipulate more explicitly the contribution of episodic memory on semantic memory performance is warranted.

In describing the nature of the disruption in semantic memory as a consequence of hippocampal amnesia, it is also important to distinguish these deficits from other disorders of semantic knowledge such as semantic dementia. Critically, the patients with amnesia here do not have a progressive neurological disorder where semantic and conceptual information degrades over time. Rather, the deficit in patients with hippocampal amnesia appears to be an inability to add significant amounts of new information to existing representations and/or an inability to establish and strengthen new relationships within and between words through their extensive, everyday use. Thus, we can view the deficit in amnesia as an impairment in protracted word learning, the ability to increase the amount of information and concepts associated with a word over time and with experience. There appears to be no degradation of basic semantic knowledge in hippocampal amnesia. Indeed, the patients were remarkably similar to the comparison participants in the features and senses they did name and there was no indication of a loss of conceptual content (i.e., all the information they provided was accurate). The amnesic patients just knew significantly less about these concepts than the comparison participants. There was also no evidence of category specific knowledge loss, which is often associated with semantic dementia. While the nature of the disruption in semantic memory reported here appears distinct from other disorders of semantic memory, future work delineating the contribution and time course of the hippocampus with the full semantic network for the acquisition and representation of semantic knowledge over time promises to offer a more complete understanding of the dynamic neural network for semantic memory and its varied disorders.

Certain limitations of this study should be noted, including the small sample size, which affects within-group comparisons in particular. In presenting the data, however, we have displayed all individual HC data points (indicating the performance of the HC and comparison groups is non-overlapping) and have used measures of effect size appropriate for small samples. The lack of volumetric analyses for extra-hippocampal structures for the whole group of amnesic patients is also a limitation. While the deficits in semantic memory presented here, as well as the other studies in the recent literature (e.g., Race et al., 2013), fit most parsimoniously with the hallmark mechanistic properties and functional processing features of the hippocampus, future work in patients with well characterized lesions to other medial temporal lobe structures is warranted to verify the anatomical specificity of our findings. Such data would also be informative in understanding the role of the hippocampus relative to other temporal lobe structures long known to support aspects of semantic knowledge.

In summary, we found that when tested with measures of semantic richness and vocabulary depth, participants with hippocampal amnesia display impoverished remote semantic memory. These deficits, on both productive and receptive measures, suggest that the hippocampus may continue to play a role in supporting semantic memory beyond its initial acquisition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grant sponsor: NIDCD; Grant number: R01 DC011755 to MCD.

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Highlights

- We examined remote semantic memory in patients with hippocampal amnesia
- We assessed semantic richness and vocabulary depth of highly familiar words
- Amnesic patients performed significantly worse than healthy and brain damaged comparison participants
- Hippocampus plays role in the maintenance and updating of semantic memory beyond its initial acquisition.

Figure 1.

Magnetic resonance scans of hippocampal patients. Images are coronal slices through four points along the hippocampus from T1-weighted scans. Volume changes can be noted in the region of the hippocampus bilaterally for patients 1846 and 2363 and significant bilateral damage to the MTL, including hippocampus, can be observed for 1951 and 2308. R = right; L = left; A = anterior; P = Posterior; NC = healthy comparison brain.

Figure 2.

Word Associates Test. Score achieved on the Word Associates Test (WAT) by amnesic participants (HC, black symbols: Patient 1846 = ■. 1951 = +. 2308 = ◆. 2363 = ●. 2563 = *) and comparison groups (with 95% CI error bars). The dotted lines represent the standard deviation from the combined comparison groups (BDC and NC).

Figure 3.

Features Task. Mean number of features per target word produced by amnesic participants (HC; black symbols: Patient 1846 = ■, 1951 = +, 2308 = ◆, 2363 = ●, 2563 = *) and comparison groups (with 95% CI error bars). The dotted lines represent the standard deviation for the combined comparison group (BDC and NC).

Figure 4. Senses Task. Senses per target word produced by amnesic participants (HC, black symbols: Patient 1846 = ■, 1951 = +, 2308 = ◆, 2363 = ●, 2563 = *) and comparison groups (with 95% CI error bars). The dotted lines represent the standard deviation for the combined comparison groups (BDC and NC).

Table 1

Demographic and neuropsychological characteristics of amnesic and comparison participants

Subject	Sex	Age	Hand	Ed	Etiology	HC Damage	HC Volume	WMS III GMI	WAIS III VIQ	WAIS III Vocab	WAIS III Info	BNT	Animals	Tools	COWA	TT
1846	F	46	R	14	Anoxia	Bilateral HC	-4.23	57	88	8	8	43	98%	89%	24	41
2363	M	53	R	18	Anoxia	Bilateral HC	-2.64	73	112	12	13	58	97%	94%	26	44
2563	M	54	L	16	Anoxia	Bilateral HC	N/A	75	91	9	12	52	100%	90%	37	44
1951	M	61	R	16	HSE	Bilateral HC +MTL	-8.10	57	107	10	11	49	96%	93%	40	44
2308	M	53	L	16	HSE	Bilateral HC +MTL	N/A	45	95	11	8	52	96%	96%	16	44
HC Mean	1F 4M	57.6 (±4.0)	3R 2L	16 (±1.4)				59.0 (±12.2)	98.8 (±10.4)	10 (±1.6)	10.4 (±2.3)	51.8 (±5.5)			28.6 (±9.8)	43.4 (±1.3)
BDC Mean	4F 1M	66.2 (±5.6)	5R	14.6 (±2.4)				116.0 (±9.7)	109.6 (±2.3)	10.6 (±1.3)	11.4 (±0.5)	56.0 (±2.9)			43.0 (±11.4)	43.8 (±0.4)
NC Mean	9F 15M	61.1 (±5.9)	19R 6L	16.3 (±1.9)				N/A	N/A	N/A	N/A	N/A			N/A	N/A

HC = hippocampus (participants with bilateral hippocampal damage). BDC = Brain-damaged comparison participants. NC = non-brain damaged comparison participants. Hand. = Handedness. Ed. = years of completed education. HSE = Herpes Simplex Encephalitis. + MTL = damage extending into the greater medial temporal lobes. N/A = no available data. Volumetric data are z-scores as measured through high resolution volumetric MRI and compared to a matched healthy comparison group (see Allen et al., 2006 for additional details). WMS-III GMI = Wechsler Memory Scale-III General Memory Index. WAIS-III VIQ = Wechsler Adult Intelligence Scale-III Verbal Intelligence Quotient. BNT = Boston Naming Test. COWA = Controlled Oral Word Association test. TT = Token Test. Bolded scores are impaired as defined as 2 or more standard deviations below normative data.

Table 2

Example responses from features task to target word menu

HC 1951	HC 2363	BDC 4	NC 7
Has the name of the place	Used to describe the foods that's going to be served by a particular eatery (3 features)	at a restaurant	Menu is most often in a place of eating (2 features)
List of foods	Allows you to select various dishes that you want to eat	given a folded list of what they serve (4 features)	A restaurant or bar or deli (3 features)
Dishes available to buy	Menu on your computer, gives you options as to what you want to do (2 features)	can look through and decide what to order for meal (3 features)	And it has all the food
Price		computers have menu with different topics you can pull them down and click on them to move yourself around on the computer system (5 features)	The prices of the appetizers, entrees, sandwiches, desserts, drinks (6 features)
Calories		cell phones have that setup where you go and pick calls and will tell you if you have missed ones (4 features)	Some are at the table some are not (2 features)
Can be on the wall		a selection, selecting this or that	Some the hostess or waitress brings you (2 features)
In a café		broken down into appetizers	It's words that you can choose to get what you like (3 features)
In a restaurant		entrees	Usually its got a plastic cover over it so nobody spills on it (2 features)
		desserts	So it's waterproof
		listing of drinks, beverages	Some hand you a day special menu
		listing for salads	With their specials on it (repetition, not a feature)
		depends on type of restaurant, they break it down differently (2 features)	Usually they have a kids menu
8 total features	6 total features	25 total features	24 features, 1 repetition

Note: Each response counted as 1 feature unless otherwise indicated.

Table 3

Example responses from senses task for word green

	HC 1846	HC 2308	BDC 2391	NC 14	NC 19
Green	Color	Color	The color	Color	Color
	Green with envy	What you shoot for on golf course	Someone that is young and innocent	Plants are called greens	Part of nature - photosynthesis
			On a golf course – the portion where the hole is	Park square	Money
			Vegetables that are this color	Not wasting energy	Eating your greens – lettuce and leafy greens
			Dollar bills can be called green	young	In harmony with the planet – not using unrenewable resources
				Inexperienced (repetition)	Adjective for technology to be better for planet (repetition)
					Not very knowledgeable , new at something
	2 senses	2 senses	5 senses	5 senses, 1 repetition	6 senses, 1 repetition

Note: Each response counted as 1 sense unless otherwise indicated.