Published in final edited form as:

J Comp Neurol. 2013 December 15; 521(18): 4356–4369. doi:10.1002/cne.23433.

Learning in Alzheimer's Disease Is Facilitated by Social Interaction

Melissa C. Duff^{1,2,*}, Diana R. Gallegos², Neal J. Cohen³, and Daniel Tranel^{2,4}

¹Department of Communication Sciences and Disorders, University of Iowa, Iowa City, Iowa 52242

²Department of Neurology, Division of Behavioral Neurology and Cognitive Neuroscience, University of Iowa, Iowa City, Iowa 52242

³Beckman Institute, University of Illinois at Urbana-Champaign, Illinois

⁴Department of Psychology, University of Iowa, Iowa City, Iowa 52242

Abstract

Seminal work in Gary Van Hoesen's laboratory at Iowa in the early 1980s established that the hallmark neuropathology of Alzheimer's disease (AD; neurofibrillary tangles) had its first foothold in specific parts of the hippocampal formation and entorhinal cortex, effectively isolating the hippocampus from much of its input and output and causing the distinctive impairment of new learning that is the leading early characteristic of the disease (Hyman et al., 1984). The boundaries and conditions of the anterograde memory defect in patients with AD have been a topic of intense research interest ever since (e.g., Graham and Hodges, 1977; Nestor et al., 2006). For example, it has been shown that patients with AD may acquire some new semantic information through methods such as errorless learning, but learning under these conditions is typically slow and inefficient. Drawing on a learning paradigm (a collaborative referencing task) that was previously shown to induce robust and enduring learning in patients with hippocampal amnesia, we investigated whether this task would be effective in promoting new learning in patients with AD. We studied five women with early-stage AD and 10 demographically matched healthy comparison participants, each interacting with a familiar communication partner. AD pairs displayed significant and enduring learning across trials, with increased accuracy and decreased time to complete trials, in a manner indistinguishable from healthy comparison pairs, resulting in efficient and economical communication. The observed learning here most likely draws on neural resources outside the medial temporal lobes. These interactive communication sessions provide a potent learning environment with significant implications for memory intervention.

© 2013 Wiley Periodicals, Inc.

*CORRESPONDENCE TO: Melissa C. Duff, Ph.D., Department of Communication Sciences & Disorders, 250 Hawkins Dr., University of Iowa, Iowa City, IA 52242. melissa-duff@uiowa.edu.

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

ROLE OF AUTHORS

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. MCD, DRG, NJC, and DT designed the study; MCD and DRG collected the data; MCD analyzed the data, and MCD, DRG, NJC, and DT wrote the article.

INDEXING TERMS

learning; memory; Alzheimer's disease; social interaction; intervention; discourse

Alzheimer's disease (AD) is a devastating neurodegenerative disease that affects a growing number of older individuals, and it is the most common form of irreversible dementia (Molloy and Lubinski, 1997). While AD may eventually result in neuropsychological deficits across multiple cognitive domains (e.g., language, attention, executive function), memory impairments are among the earliest and most frequently reported symptoms of AD. The hallmark deficit in the early stages of AD is a profound impairment in acquiring new declarative memory for both semantic (facts, vocabulary) and episodic (events of daily life) information (Hyman et al., 1984, 1990; Eichenbaum and Cohen, 2001). The observed memory impairment is consistent with evidence suggesting that early pathological involvement is localized in the mesial temporal lobes, especially in the hippocampal formation and entorhinal cortices (Hyman et al., 1984; Braak and Braak, 1990; Van Hoesen et al., 1991). In fact, the seminal work by Gary Van Hoesen and his colleagues at Iowa showed that cellular loss (and corresponding buildup of neurofibrillary tangles) in the subiculum of the hippocampal formation and in layers II and IV of the entorhinal cortices effectively isolated the hippocampal formation from its inputs and outputs with association cortices, basal forebrain, thalamus, and hypothalamus (Hyman et al., 1984). This work provided a compelling account of the anterograde memory impairment in AD, which the authors emphasized in their initial reports (Hyman et al., 1984, 1986, 1990; Van Hoesen et al., 1991). This work fueled decades of subsequent research on related themes, which has elaborated and refined the original messages—but as we sit here today, the path-breaking discoveries from Van Hoesen's laboratory have stood well over the test of time, and the essential story has not changed.

Although there is no known cure for AD there have been modest advances in pharmacological treatments to ameliorate symptoms or slow the progression of the disease and in behavioral techniques (e.g., spaced retrieval, vanishing cues, errorless learning) to promote learning and/or to compensate for lost function (e.g., McKittrick et al., 1992; Clare et al., 1999, 2000; Bourgeois et al., 2003; Evans et al., 2004; Desai and Grossberg, 2005). These highly structured behavioral techniques are indeed successful in facilitating some new semantic learning (e.g., face-name pairings) in memory-impaired patients, including patients with AD. The learning, however, is far from normal. Memory impaired participants learn less and show less rapid learning than healthy participants (i.e., memory impaired individuals require many more trials to acquire only a fraction of what healthy participants can learn) (e.g., Bayley and Squire, 2002; O'Kane et al., 2004; Skotko et al., 2004). Furthermore, generalization tends to be quite poor (e.g., Stark et al., 2005).

Of particular interest to the current study are the similarities in the nature of the memory impairments of patients in the early stages of AD and individuals with anterograde hippocampal amnesia (another theme emphasized in the studies emanating from Van Hoesen's laboratory; e.g., see Van Hoesen, 1997). In fact, the conceptual groundwork for many of the behavioral techniques used clinically with AD patients today was laid and

further developed experimentally with patients with hippocampal amnesia (e.g., Warrington and Weiskrantz, 1970; Glisky et al., 1986; Squire et al., 1997). Along these lines, using a collaborative referencing paradigm to investigate the ability of individuals with hippocampal amnesia to acquire and use referential labels for novel picture cards across repeated collaborative and dynamic interactions with a familiar partner, we reported a normal rate of learning in individuals with amnesia (Duff et al., 2006). In our study, participants with bilateral hippocampal damage and severe declarative memory impairment worked with a familiar communication partner to establish a shared perspective and set of unique references for a set of 12 abstract figures (Chinese tangrams). The task was framed as a game and the participant pairs were told to have fun. The participants with amnesia directed their familiar communication partner on how to arrange the cards a total of 24 times across 2 days. We also tested subsequent memory retention for the labels, outside of the context of the task.

We found that despite severe declarative memory impairments, amnesic participants showed robust collaborative learning across trials. Although the amnesic participants were slower overall and used more words across trials than demographically matched comparison participants, the rate of learning across trials was equal to that of the healthy comparison subjects (Duff et al., 2006). The amnesic participants' learning resulted in their arriving at labels that facilitated increasingly efficient communication as they used increasingly fewer words to reference the cards on each trial. Impressively, learning of the labels endured long after the task ended as measured at 30-minute and 6-month intervals (and at 2 years for one participant).

Here we extend this work to examine whether patients with AD demonstrate robust learning of referential labels when engaged in collaborative and social interaction. The goal of the present study was to examine whether a collaborative referencing paradigm, which promotes collaboration and social interaction, would facilitate learning in patients with AD. Using the same experimental design as Duff et al. (2006) we tested the hypothesis that, like patients with dense and circumscribed memory impairments from hippocampal amnesia and their partners, the performance of participants with AD and their communication partners would demonstrate learning in the collaborative referencing task and that the learning would not differ from healthy comparison participants.

PARTICIPANTS AND METHODS

Participants

Participants included five AD pairs (individuals with AD and their familiar partners) and 10 comparison pairs (healthy participants and their familiar partners). Participants were recruited from the Benton Neuropsychology Clinic at the University of Iowa and the Iowa City, Iowa community. All participants were compensated and gave informed consent, which was approved by the Institutional Review Board of the University of Iowa.

The AD participants were all right-handed women who were, on average, 77.0 years old ($SD = 5.4$; range = 71–84 years) and who had, on average, 14.8 years of education ($SD = 3.3$; range 12–20 years). Diagnoses of probable AD were made by a neuropsychologist and

neurologist and were based on the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's and Related Disorders Association (NINCDS) criteria (McKhann et al., 1984). (Note that these criteria have since been updated: McKhann et al., 2011; the data presented here were collected prior to 2011 and thus the 1984 criteria were used.) AD severity was determined to be very mild, or 0.5, for all five participants based on the Washington University Clinical Dementia Rating (CDR) scale (Morris, 1993). Although AD patients had a CDR classification of very mild, neuropsychological testing revealed that all participants had severe declarative memory impairments and scattered deficits in other domains. Table 1 presents neuropsychological data in the domains of memory, language, executive function, and visual spatial ability from standardized measures. All AD participants began the study within 1 month of their diagnosis of probable AD.

The 10 healthy comparison participants were matched to the AD participants on age, education, sex, and handedness. There were no significant group differences on age, $t(13) = 1.244$, $P = 0.235$, or education, $t(13) = -0.211$, $P = 0.836$. Comparison participants had normal or corrected to normal vision and hearing, and no history of neurological disease or learning disabilities, per self-report.

Each of the AD and comparison participants selected a familiar communication partner with whom they completed all trials of the collaborative referencing task. Familiar partners were required to have at least 2 years of frequent communication with the participant, although the length of communicative history was much longer for many pairs (e.g., spouses). The familiar partners for the AD participants were two spouses, a daughter, a niece, and a friend. For the comparison participants, the partners were three spouses, a daughter, a granddaughter, and five friends. Familiar communication partners had normal corrected vision and hearing, and a negative history of neurological disease and learning disabilities, per self-report. The familiar partners of the AD participants were, on average, 62.6 years old (range = 54–72) and had, on average, 15.6 years of education. The familiar partners of the comparison participants were, on average, 65.9 years old (range = 22–84) and had, on average, 15.6 years of education. There were no significant differences between the familiar partners of the AD and comparison participants for age ($t(13) = 0.605$, $P = 0.556$) or education ($t(13) = 0.331$, $P = 0.746$).

All comparison participants and familiar partners were screened to be free of dementia using the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). Inclusion criterion was 27 out of 30 on the MMSE (e.g., Kukull et al., 1994). Mean MMSE of the comparison participants, familiar partners of comparison participants, and familiar partners of AD participants were 29.4, 29.2, and 29.8, respectively.

Procedures

Collaborative referencing task—Procedures for the collaborative referencing task were identical to those in Duff et al. (2006). To complete the task, participant pairs sat at a table facing each other and each member of the pair had boards with 12 numbered spaces and identical sets of 12 playing cards displaying Chinese tangrams. These tangram figures are complex, black and white geometric shapes which can resemble human figures, but have no established names. A partial barrier obscured the view of the others' stimulus cards but

allowed participants to see each others' facial expressions and gestures. Figure 1 displays the setup with the tangram figures. The participants with AD (and the comparison participants) were the directors and the familiar communication partners were the matchers. At the beginning of each trial the director (participants with AD) had the 12 cards in a unique sequence for each trial that was predetermined by the investigator. The director communicated to the matcher how to set up his/her board using the cards so that at the end of the trial the two boards looked alike. The matcher began with her/his cards set around the board so that they were easily viewed and reached. The task was presented as a game and participants were told to have fun. Participants were instructed to communicate as much as needed to successfully complete the game but that they could not move the barrier or stand up to look at the order of the cards on each others' board. The experimenter left the room while the pairs played the game and feedback was only provided after each trial regarding the total number of correct card placements. To reduce participant fatigue, a concern observed during pilot testing, we modified the Duff et al. (2006) design to reduce the number of trials from 24 (six trials in each of four sessions, two sessions per day) to 12 (six trials in each of two sessions on the same day). All sessions were videotaped and the time to complete each trial and the number of correct card placements were recorded.

Thirty minutes after the last session, the experimenter conducted a delayed memory test with the directors (AD participants), outside of the context of the task and without the familiar communication partner, to assess his/her memory of the cards and the labels generated during the sessions. The delayed memory test was a yes/no recognition test with 24 tangram picture cards, 12 *old* (from the task) and 12 *new* (foils). Participants were shown the cards used in the task, asked if each card was familiar, and asked to generate a label for each card. Directors were reassessed again 2 weeks later in the same fashion.

Transcribing the collaborative interactions—Video recordings of the collaborative referencing task yielded more than 17 hours of videotaped data for analysis. Transcription conventions followed those used in our previous studies (Duff et al., 2006, 2008). Only the experimental trials (not task instructions or conversations between trials) were transcribed. Transcript preparation involved three stages performed by an original and consensus transcriber. In the first stage, the audio portion of the taped interactions was transcribed by the original transcriber who listened to the audiotape and transcribed all utterances, audible sounds, and pause times. In the second stage, the original transcriber watched the videotaped interactions and added card placements and made corrections to the audio content of the transcript. In the third stage, the consensus transcriber and the original transcriber viewed the video together and generated a final version of the transcript: the consensus transcription. Corrections and additions were made through discussion and consensus.

Coding communicative resources—We analyzed data from the transcripts to quantify the number of words and the number of interactional turns across each of the 12 trials and by both participants (AD patient and familiar partner) in a pair. *Interactional turns* were defined as utterances produced by one individual and could include both verbal and nonverbal resources, or consist of a gesture or nonverbal back-channel response (e.g., head nod) alone. Turn boundaries were denoted by a change in speaker. When two individuals

spoke simultaneously, each speaker's utterance was counted as a turn. Words were broadly defined with little emphasis placed on morphological or syntactic form. Each word in a false start was counted (e.g., *they should have, they are both facing right* = 8 words). Fillers (e.g., *uh* = 1 word), contractions (e.g., *don't* = 1 word) and verbal back-channel or continuer responses (e.g., *uh huh* = 1 word) were each counted as one word.

Alien-word paired-associate learning control task—In contrast to the collaborative referencing task, the control task did not require participants to self-generate the perspectives and labels and eliminated the collaborative and dynamic social interaction. A set of 12 black and white line drawings of space aliens that had no preestablished names were arbitrarily paired with words from the word list A of the Wechsler Memory Scale-III. Figure 2 displays the 12 alien-word pairs (Gupta et al., 2004). Participants were asked to learn the alien-word pairs across the same training schedule as used in the collaborative referencing task (across 12 trials, with six trials in each of two sessions on the same day). The experimenter presented each alien visually and the paired word orally, at the rate of one alien-word pair per 3 seconds. After all 12 alien-word pairs were presented, the participants were shown each alien in succession and were asked to supply the paired word for each from memory, as in standard paired-associate learning. The alien-word pairs were presented in a different random sequence on each trial. Memory testing for the alien-word control task was conducted in the same fashion as the memory testing for the collaborative referencing task (e.g., yes/no recognition testing and free recall of paired words for each card at 30 minutes and 2 weeks).

The two collaborative referencing sessions and the two alien-word associate learning sessions were conducted on the same day. All participants performed the first session of the collaborative referencing task first followed by the first session of the alien-word task. After a 30-minute break, all participants performed the second session of the collaborative referencing task followed by the second session of the alien-word task. After another 30-minute break, AD and comparison participants performed the subsequent memory tests outside of the context of the collaborative referencing task and without their familiar communication partners.

Reliability of coding

Inter- and intrarater reliability were obtained for the word and interactional turn coding from the collaborative referencing task for approximately 16% of the data (two trials randomly selected per pair). Inter- and intra-rater reliability for the number of words and turns were 0.91 and 0.99, and 0.99 and 0.99, respectively. Inter- and intrarater reliability for the initiating noun phrase coding was 0.98 and 0.96, respectively.

RESULTS

Collaborative referencing task

Card placement accuracy—Both AD and comparison pairs successfully completed all trials, with 95.0% and 96.4% overall card placement accuracy, respectively.

Time to completion—Across trials, both within and across sessions, AD and comparison pairs displayed marked reductions in the time to complete each trial. Mean time to completion for the set of 12 tangram cards dropped from 10:07 (min:sec) and 11:06 min on trial 1 for AD and comparison pairs, respectively, to just 1:41 min and 1:16 min on the final trial. A repeated-measures analysis of variance (ANOVA) showed significant learning across trials ($F_{5, 65} = 25.521, P < 0.001$) and pairs were indistinguishable in their time to complete the trials (no main effect of group: $F_{1, 13} = 0.211, P = 0.654$). Figure 3a displays the time to completion by group.

Communicative resources for referencing the cards—Across trials, there was also a stark reduction in the communicative resources required to complete the task. This was seen as a sharp drop in the number of interactional turns and total words used across the interactive trials. The mean number of interactional turns dropped from 194.8 and 174.2 on trial one for AD and comparison pairs, respectively, to 44.8 and 31.8, respectively, on trial 24. We observed significant learning across trials (repeated-measures ANOVA; $F_{5, 65} = 20.932, P < 0.001$) and pairs did not differ in the overall number of turns (no main effect of group: $F_{1, 13} = 0.591, P = 0.456$). The mean number of words dropped from 1,441.6 and 1,612.5 on trial one for AD and comparison pairs, respectively, to 271.2 and 166, respectively, on trial 24. Again, we observed significant learning across trials (repeated-measures ANOVA; $F_{5, 65} = 19.267, P < 0.001$) and pairs did not differ in the overall number of words (no main effect of group: $F_{1, 13} = 0.202, P = 0.661$). Figure 3b displays the reduction in the total number of words across trials by group.

On the first trial, there was extended back and forth negotiation as partners described the tangrams, discussed the rules and procedures of the task, and commented on their successes and difficulties. Table 2 shows this extended discourse as an AD participant and her partner work to place the first card on trial one. By contrast, the referencing expressions of the same cards by the same AD participant and partner on the 12th trial were remarkably more concise and efficient, as shown in Table 3.

The majority of card descriptions generated by the AD participant on that final trial were simple and streamlined, and there was minimal contribution from the partner in order to place most of the cards on that final trial. The relative contribution of the familiar communication partners across the interactions was remarkably similar for the AD and comparison pairs. Examination of the total word counts revealed that across the 12 trials the partners of the AD and comparison pairs contributed 39.3% and 40.8%, respectively, of the total words to the interactions. The familiar partners decreasing role across trials was also similar with partners contributing 41.1% and 43.8% of the total words on trial 1 for AD and comparison pairs, respectively, and 29.3% and 27.7%, respectively, on trial 12. Thus, the partners in the AD groups were not carrying more of the communicative burden.

Retention—We conducted a delayed memory test for recognition of the tangram cards and recall of the card labels at a 30-minute delay and during a 2-week follow-up with the directors (participants with AD) outside the context of the task and without the familiar communication partner. At the 30-minute delay, each AD participant correctly recognized all 12 (100%) tangram cards that were used in the collaborative referencing task and as a

group had a low rate of false positives (incorrect endorsement) on the foils ($n = 3$, or 5%). AD participants were able to produce the same labels they used to reference the cards in the task for 9.4 of the tangrams (range = 7–12), on average, or 84%. Comparison participant performance was very similar. At the 30-minute delay, comparison participants recognized 11.8 (98%) tangrams, on average, and had no false positives. At the 30-minute delay, comparison participants were able to generate the same labels they used in the collaborative referencing task for 10.8 of the tangrams (range = 9–12), on average, or 90%.

At the 2-week follow-up AD participants recognized 11.4 tangrams, on average, or 95% with 11 total false positives on the foils (18%). AD participants were still able to produce the same labels they used to reference the cards in the task for 9.6 of the tangrams (range = 7–11), on average, or 84%. Healthy comparison participants recognized 11.6 tangrams, on average, or 97% with two total false positives on the foils (3%). At that time, comparison participants produced the same labels they used to reference the cards in the task for 9.9 of the tangrams (range = 6–12), on average, or 83%.

Alien-word paired-associate learning control task

In marked contrast to their performance on the collaborative referencing task, performance of the AD patients on the alien-word pairs was notably impaired. The comparison participants quickly learned the pairs and reached ceiling performance by the 11th trial. The AD participants, however, attained only 2.6 out of 12, on average, by the end of the 12 trials. The impairment on the alien-word pairs was seen as a significant main effect of group ($F_{1, 13} = 306.8$, $P < 0.001$) and a significant interaction of group with learning across trials ($F_{5, 65} = 10.758$, $P < 0.001$).

Retention—At the 30-minute delay, the AD participants recognized, on average, 10.8 (90%) of the aliens (range = 9–12) that were used in the control task and as a group had 15 (25%) false positives (incorrect endorsement) on the foils. Consistent with the poor performance of AD participants acquiring the arbitrary, experimenter-generated labels for the aliens, the AD participants, on average, were only able to recall 1.4 (12%) of the labels (range = 0–4) at the 30-minute delay. Comparison participant performance, particularly recall, was much stronger. At the 30-minute delay the comparison participants recognized all 12 (100%) aliens, on average, and had no false positives. Comparison participants were able to generate the same arbitrary, experimenter-generated labels learned in the control task for 11.8 of the aliens (range = 11–12), on average, or 98%.

At the 2-week follow-up, AD participants recognized, on average, 8.4 (70%) of the aliens (range = 6–10) that were used in the control task and as a group had 17 (28%) false positives (incorrect endorsement) on the foils. AD participants were only able to recall 0.4 (3%) (range = 0–2) of the labels for the aliens at the 2-week follow-up. At the 2-week follow-up, the comparison participants recognized 11.7 of the aliens (range = 11–12), on average, or 98% with six total false positives on the foils (10%). Comparison participants, on average, were able to recall 9 (73%) (range = 7–12) of the labels for the aliens.

Comparison to patients with hippocampal amnesia

Given the similarities in the observed memory impairment of patients with AD and those with anterograde hippocampal amnesia and the robust learning displayed by the patients with amnesia in our earlier work, we were interested in comparing the two groups' performance on the collaborative referencing task. For this analysis, we examined the performance of three patients with bilateral hippocampal damage due to an anoxic/hypoxic episode (cardiac arrest in two cases, and an allergic reaction leading to status epilepticus in the other case) and profound anterograde amnesia originally reported in Duff et al. (2006). The amnesic patients included two males and at the time of the original study these patients were 49.6 (SD = 3.7) years old, on average, had 13.6 (SD = 4.0) years of education, on average, and were in the chronic epoch of their amnesia with time post onset ranging from 3 to 5 years. The three amnesic patients were significantly younger than the five AD participants, $t(6) = -7.519$, $P < 0.001$, but no significant differences for education were observed, $t(6) = -0.432$, $P = 0.681$.

Like the patients with AD, all the amnesic patients had memory impairments that were sufficiently severe to interfere with daily life and all exhibited severe memory impairment on standardized tests of memory. Performance on the Wechsler Memory Scale-III was at least 25 points lower than their performance on the Wechsler Adult Intelligence Scale-III (mean FSIQ-WMS-MQ difference = 29.3), with an average delay score on the memory scale (67.3) that was more than 2 SDs below population means. The amnesic patients were severely impaired in delayed recall on the Rey Auditory Verbal Learning Test; only one patient could report even a single item (out of 15) despite multiple study opportunities ($M = 0.33$). Performance on delayed recall on the Complex Figure Test was also impaired for amnesic patients; mean performance was 4.6 out of 36. These severe memory impairments are comparable to those of the AD patients whose mean delayed recall on the California Verbal Learning Test and Complex Figure Test were 1.4 (out of 16) and 5.2 (out of 36), respectively. Unlike the participants with AD, the memory impairments in amnesia are observed in the context of relatively persevered intelligence and other cognitive functioning such as attention, reasoning, and language. The collaborative referencing task completed by the amnesia patients and their familiar communication partners was identical to that of AD patients with the exception that amnesia patients had an additional 12 trials (total of 24 trials) on a consecutive day of testing. For the analysis presented here we will only look at the first 12 trials.

Despite the differences in age and additional cognitive disruptions in AD, performance of the AD pairs and amnesia pairs on the collaborative referencing task was remarkably similar. For both groups, across trials there is reduction in the amount of time required to complete each of the trials. Mean time to completion for the set of 12 tangram cards dropped from 10:07 (min:sec) and 13:46 min on trial 1 for AD and amnesia pairs, respectively, to just 1:41 min and 4:10 min on the twelfth trial. Repeated-measures ANOVA showed significant learning across trials ($F_{5, 30} = 12.940$, $P < 0.001$) and although amnesic pairs were slower on the first and last trial, there was no main effect of group ($F_{1, 6} = 2.93$, $P = 0.138$). It is worth mentioning that the increased time observed for the amnesia pairs during

the second session (trials 7–12) was attributable to one amnesic patient who was particularly fatigued while the times for the other two amnesia pairs were in line with the AD pairs.

Similarly, both groups showed the same pattern of reduction in the total number words across trials. Mean number of total words produced cards dropped from 1,442.0 and 1,404.0 on trial 1 for AD and amnesia pairs, respectively, to just 271.2 and 421.0 on the twelfth trial. Repeated-measures ANOVA showed highly significant learning across trials ($F_{5, 30} = 10.222$, $P = 0.003$) and there was no main effect of group ($F_{1, 6} = 238.0$, $P < 0.001$). Again, the higher mean total number of words on the final trial for the amnesic pairs was due to the one fatigued amnesic patient and the other two amnesic pairs were in line with the AD pairs. Figure 4 displays the reduction in time and number of words across trials for participant pairs with AD and amnesia.

DISCUSSION

The successful learning observed here is in stark contrast to the deficits shown by these and other patients with AD in tests of memory for new semantic information. One critical difference between our collaborative referencing task and the majority of other semantic learning tests is that participants were not required to learn arbitrarily related, experimenter-generated labels. Instead, participants draw on preexisting semantic knowledge to self-generate appropriate and meaningful card labels such as “sleeper” for a figure that could be seen as a person sleeping. Thus, in the absence of the requirement to acquire arbitrary relations, the participants with very mild AD performed as well as healthy comparison participants. However, when faced with acquiring arbitrarily paired associations, as was the case in the control experiment, the AD patients displayed the severe learning and memory impairments that we routinely associate with hippocampal dysfunction and episodic memory impairment. These results are consistent with work emphasizing the role of the hippocampus in, and the nature of antero-grade memory impairment for, the binding together of arbitrary relations (Eichenbaum and Cohen, 2001; Rosenbaum et al., 2009).

Despite distinct etiologies and significant age differences between the participants with AD and the participants with hippocampal amnesia from our previous study, their performance on the collaborative referencing, as measured by time and communicative resources, was indistinguishable (Duff et al., 2006). This finding makes good sense given the similarities in anterograde declarative memory caused by damage or pathology to the hippocampal system in the medial temporal lobes in early-stage AD and hippocampal amnesia (McKhann et al., 1984; Braak and Braak, 1990; Van Hoesen et al., 1991; Eichenbaum and Cohen, 2001). The observed learning here most likely draws on neural resources outside the medial temporal lobes. Given the gradual and normal rate of learning, the mechanisms of learning are most consistent with those of the nondeclarative memory system. This interpretation would be in line with our work in amnesia and research demonstrating intact nondeclarative memory in patients with mild AD (Hirono et al., 1997; Duff et al., 2006).

There are, however, some notable differences between our two studies. Participants with hippocampal amnesia had a *rate* of learning that did not differ from their demographically matched comparisons, but amnesic participants were slower overall and used more words,

on average, than healthy participants across all trials. This difference was not observed between AD and healthy participants; performance on all measures was overlapping. Given the similar performance between participants with AD and amnesia, we suspect this difference may be an affect of age in the comparison participants. That is, the healthy comparison participants in the amnesia study (mean age = 49) were faster and used fewer communicative resources than AD and amnesia participants and the healthy older comparison participants in the current study (mean age = 77). This interpretation would be consistent with research reporting poorer performance on a collaborative referencing task in older adults compared to younger adults (Hupet et al., 1993; Filer and Scukanec, 1995).

In separate analyses of the amnesia and AD collaborative referencing datasets, we examined the use of verbal play, the playing with the sounds and meanings of words through the use of puns, voices and sound effects, teasing, and telling funny stories or jokes in communication (Duff et al., 2009; Shune and Duff, 2012). In our study of verbal play in amnesia we found that the amnesia participants produced significantly fewer verbal play episodes than their demographically matched healthy comparison participants (Duff et al., 2009). In contrast, there were no differences in the use of verbal play in the interactions of the AD participants (Shune and Duff, 2012). That is, participants with AD produced verbal play episodes that were similar in quantity and quality to the healthy comparison participants. While performance on the learning variables do not differentiate participants with amnesia from participants with AD, the richness of the social interactions with their familiar communication partners does. One possible explanation is that patients with hippocampal amnesia have a more severe memory impairment than individuals in the very early stage of AD and that these deficits are not captured by neuropsychological testing (i.e., both groups are near floor levels on standardized memory tests). Furthermore, there is evidence that the extent of hippocampal pathology may be greater in patients with amnesia than in mild AD (Gold and Squire, 2005; Schuff et al., 2009). Since nondeclarative memory mechanisms most likely support the observed learning here, we would not necessarily expect differences in hippocampal structure or function to affect learning performance on this task. Another possibility is that differences between the onset of the memory impairment (sudden vs. progressive) and the length of time the communication pairs have been managing the memory impairment contribute to the quality of the social interaction. The amnesia participants became memory impaired after a sudden neurological event (e.g., anoxia episode) and at the time of the study had been managing the memory impairment, and its consequences, for years (3–18 years). In contrast, the participants with AD were recently diagnosed (within 1 month) and had a gradual onset of memory decline that was perhaps initially interpreted in the context of normal aging. Future research is warranted to further examine these interpretations, as the results may illuminate the interactions between neural pathology, cognitive performance, and the quality of social and communicative interactions. Such outcomes have important implications for basic science and for rehabilitation, counseling, and training communication partners. Indeed, given the highly successful performance of the participants with AD in this social, collaborative task and the preserved use of verbal play in their social interactions, enriching the communicative interactions of individuals with AD and their caretakers (family or staff) by incorporating verbal play and

other opportunities for social interaction may have therapeutic and interpersonal benefits (see below).

Although this study is the first to report fully intact learning in a collaborative referencing task with patients with AD, it is not the first to employ this paradigm in patients with AD. In fact, there have been several studies using a version of this task with AD patients, although the focus of those studies was on communication abilities rather than learning per se (e.g., Carlomagno et al., 2005; Feyereisen et al., 2007). In Carlomagno et al. (2005) AD participants (described as mild to moderate) described line drawings in one trial of a collaborative referencing task to an examiner and their productions were judged to be less efficient (e.g., more words, less crucial information, more errors) than healthy controls. In Feyereisen et al. (2007), AD participants (described as very mild and mild) described six tangrams to the experimenter across three trials and were found to produce significantly more words and turns overall.

There are several factors that likely contribute to the difference between these studies and the current work, where performance of participants with AD did not differ from healthy comparison participants. One difference could be disease severity. The AD participants in our study were all determined to have very mild AD as measured by the CDR (Morris, 1993), whereas participants in the other studies were judged to be mild to moderate and very mild to mild (Carlomagno et al., 2005; Feyereisen et al., 2007). In addition to declining memory performance (likely associated with decreasing hippocampal volume; e.g., Schuff et al., 2009), increased severity may also be associated with greater disruptions in linguistic and communicative abilities (e.g., Appell et al., 1982; Orange and Colton-Hudson, 1998; Salmon et al., 1999; Bayles and Tomoeda, 2007; Bourgeois and Hickey, 2009). The use of semantic knowledge appears to be an important component of successful performance in these tasks. Although deficits in semantic knowledge can be detected in the very early stages of AD (e.g., Adlam et al., 2006) such impairments become more evident and severe with disease progression and with advancing pathology outside the medial temporal lobe (Hodges and Patterson, 1995; Giffard et al., 2001). We suspect that the more significant linguistic, semantic, and discursive impairments associated with the increased severity could play a role in the different outcomes. Systematic study of individuals with AD who are well-characterized neuropsychologically and at various stages of the disease is warranted.

There are also significant methodological differences between studies that may contribute to the different findings. The Carlomagno et al. (2005) and Feyereisen et al. (2007) studies both had a limited number of trials (1–3) and employed a full barrier that prevented the participants with AD from seeing the examiner, whose communication was scripted. To optimize learning in our version of the collaborative referencing task, we made a number of modifications to the earlier protocols in the literature (e.g., Clark and Wilkes-Gibbs, 1986) in an attempt to preserve the naturalistic and emergent aspects of social interaction (see Duff et al., 2008). These modifications included using a partial barrier so participants could utilize nonverbal communication (e.g., facial expressions, gesture), increasing the number of learning opportunities (12 trials in the current study), and using familiar partners who were encouraged to have fun and communicate freely. We suspect these methodological differences significantly impact learning and communication. Indeed, in conducting this

study and analyzing the data, we were struck by how much the AD participants and their partners clearly enjoyed the collaborative referencing task based on their self-reports (e.g., *Can we keep playing*) and demonstrated by their positive and playful behavior (e.g., high fives, laughter, smiles) displayed throughout these interactive sessions. (It is interesting to note that these playful behaviors, as well as the use of verbal play describe above, are not mentioned in other studies of collaborative referencing that employ the full barrier and stranger or confederate partners.) Yet as the disease progresses identification of resources and strategies that allow individuals with AD to remain as functional and socially integrated as possible becomes a primary goal of management, as there is impoverished and reduced opportunities for interactional engagement (e.g., Ramanathan, 1997; Yorkston et al., 2010).

We have advocated for the development of *rich communicative environments* that support opportunities for active learning and the co-construction of socially complex, collaborative engagement (see Duff et al., 2007, 2008; Hengst and Duff, 2007). Whereas traditional interventions often target the impairments of an individual, we suggest interventions targeted at structuring and creating diverse opportunities for learning and interactional enrichment and engagement through meaningful, goal-directed communication and social interaction (see Hengst et al., 2010). Such an approach is warranted for individuals with profound impairments in memory and learning where memory function will not be restored and extends to populations where there is progressive deterioration (e.g., dementia).

Converging evidence across animal, human, and clinical populations point to the benefits of enrichment, social interaction, and engagement (e.g., van Praag et al., 2000; Nithianantharajah and Hannan, 2006; Hertzog et al., 2008). Indeed, meaningful social interaction and engagement may provide a physical, cognitive, and psychosocial buffer from the negative changes associated with healthy and pathological aging (e.g., Adams and McGuire, 1986; Tennant, 1990; Solomon, 1996; Bassuk et al., 1999; Hertzog et al., 2008; Tse et al., 2010). Research suggests that social network size modifies the association between AD pathology and cognitive functioning. Bennett et al. (2006) found that, even for individuals with severe disease pathology, cognitive functioning remained higher in those individuals with AD who had larger social networks (e.g., number of friends and family members with whom they have at least monthly contact). Furthermore, the affective benefits of engagement and interaction can be long-lasting. For example, we have shown that the feeling of emotion can endure beyond the conscious recollection for the events that initially triggered the emotion, suggesting that the benefits of a positive interaction or hearing a funny story endure after the visit is over and the punchline is forgotten (Feinstein et al., 2010).

In summary, this line of research on the nature of spared and impaired learning in patients with AD builds on Gary Van Hoesen's seminal work localizing the early pathological involvement in AD to the mesial temporal lobes, specifically hippocampal formation and entorhinal cortices, causing the impairment of new learning that is the hallmark early characteristic of the disease. Indeed, the participants with AD we studied here had profound deficits in acquiring arbitrary relations (in the control experiment) that we routinely associated with the hippocampal pathology and episodic memory impairment of AD. However, at the heart of this report is the significant and enduring learning we observed in

individuals with very mild AD when they are engaged in collaborative and social interaction with a familiar communication partner. Drawing on neural resources outside the mesial temporal lobes, these interactive communication sessions provide a potent learning environment with significant implications for memory intervention.

Acknowledgments

Grant sponsor: Fraternal Order of the Eagles; Grant sponsor: NIDCD; Grant number: 1F32DC008825; Grant sponsor: Program Project Grant NINDS; Grant number: NS 19632.

We thank B. Bachelder and J. St. John for transcribing the sessions and assistance in data coding and analysis.

LITERATURE CITED

- Adlam AL, Bozeat S, Arnold R, Watson P, Hodges JR. Semantic knowledge in mild cognitive impairment and mild Alzheimer's disease. *Cortex*. 2006; 42:675–684. [PubMed: 16909626]
- Appell J, Kertesz A, Fisman M. A study of language functioning in Alzheimer's patients. *Brain Lang*. 1982; 17:73–91. [PubMed: 7139272]
- Bassuk S, Glass T, Berkman L. Social disengagement and incident cognitive decline in community-dwelling elderly persons. *Ann Intern Med*. 1999; 131:165–173. [PubMed: 10428732]
- Bayles, KA.; Tomoeda, CK. Cognitive-communication disorders of dementia. San Diego: Plural Publishing; 2007. Alzheimer's dementia; p. 55-74.
- Bayley P, Squire L. Medial temporal lobe amnesia: gradual acquisition of factual information by nondeclarative memory. *J Neurosci*. 2002; 22:5741–5748. [PubMed: 12097527]
- Bennett DA, Schneider JA, Tang Y, Arnold SE, Wilson RS. The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study. *Lancet Neurol*. 2006; 5:406–412. [PubMed: 16632311]
- Bourgeois, MS.; Hickey, EM. Dementia: from diagnosis to management — a functional approach. New York: Psychology Press; 2009.
- Bourgeois MS, Camp C, Rose M, White B, Malone M, Carr J, Rovine M. A comparison of training strategies to enhance use of external aids by persons with dementia. *J Commun Disord*. 2003; 36:361–378. [PubMed: 12927944]
- Braak H, Braak E. Neurofibrillary changes confined to the entorhinal region and an abundance of cortical amyloid in cases of presenile and senile dementia. *Acta Neuropathol*. 1990; 80:239–259.
- Braak H, Braak E. Staging of Alzheimer's disease related neurofibrillary changes. *Neurobiol Aging*. 1995; 16:271–284. [PubMed: 7566337]
- Carlomagno S, Santoro A, Menditti A, Pandolfi M, Marini A. Referential communication in Alzheimer's type dementia. *Cortex*. 2005; 41:520–534. [PubMed: 16042028]
- Clare L, Wilson BA, Breen K, Hodges JR. Errorless learning of face-name associations in early Alzheimer's disease. *Neurocase*. 1999; 5:37–46.
- Clare L, Wilson BA, Carter G, Gosses A, Breen K, Hodges JR. Intervening with everyday memory problems in early Alzheimer's disease: an errorless learning approach. *J Clin Exp Neuropsychol*. 2000; 22:132–146. [PubMed: 10649552]
- Clark H, Wilkes-Gibbs D. Referring as a collaborative process. *Cognition*. 1986; 22:1–39. [PubMed: 3709088]
- Desai AK, Grossberg GT. Diagnosis and treatment of Alzheimer's disease. *Neurology*. 2005; 64(Suppl 3):34–39.
- Duff MC, Hengst J, Tranel D, Cohen NJ. Development of shared information in communication despite hippocampal amnesia. *Nat Neurosci*. 2006; 9:140–146. [PubMed: 16341214]
- Duff MC, Hengst J, Tranel D, Cohen NJ. Talking across time: using reported speech as a communicative resource in amnesia. *Aphasiology*. 2007; 21:702–716.
- Duff MC, Hengst J, Tranel D, Cohen NJ. Collaborative discourse facilitates efficient communication and new semantic learning in amnesia. *Brain Lang*. 2008; 106:41–54. [PubMed: 18078671]

- Duff MC, Hengst J, Tranel D, Cohen NJ. Hippocampal amnesia disrupts verbal play and the creative use of language in social interaction. *Aphasiology*. 2009; 23:926–939. [PubMed: 20300442]
- Eichenbaum, H.; Cohen, NH. From conditioning to conscious recollection: memory systems of the brain. New York: Oxford University Press; 2001.
- Evans JG, Wilcock G, Birks J. Evidence-based pharmacotherapy of Alzheimer's disease. *Int J Neuropsychopharmacol*. 2004; 7:351–369.
- Feinstein JS, Duff MC, Tranel D. Sustained experience of emotion after loss of memory in patients with amnesia. *Proc Natl Acad Sci U S A*. 2010; 107:7674–7679. [PubMed: 20385824]
- Feyereisen P, Berrewaerts J, Hupet M. Pragmatic skills in the early stages of Alzheimer's disease: an analysis by means of a referential communication task. *Int J Lang Commun Disord*. 2007; 42:1–17. [PubMed: 17365083]
- Filer L, Scukanec G. Collaborative referencing in elderly women. *Percept Motor Skills*. 1995; 81:995–1000. [PubMed: 8668464]
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12:189–198. [PubMed: 1202204]
- Glisky EL, Schacter DL, Tulving E. Computer learning by memory impaired patients: Acquisition and retention of complex knowledge. *Neuropsychologia*. 1986; 24:313–328. [PubMed: 3755511]
- Gold J, Squire L. Quantifying medial temporal lobe damage in memory-impaired patients. *Hippocampus*. 2005; 15:79–85. [PubMed: 15390163]
- Graham KS, Hodges JR. Differentiating the roles of the hippocampal complex and the neocortex in long-term memory storage: evidence from the study of dementia and Alzheimer's disease. *Neuropsychology*. 1997; 11:77–89. [PubMed: 9055272]
- Gupta P, Lipinski J, Abbs B, Lin P, Aktunc E, Ludden D, Matin N, Newman R. Space aliens and nonwords: stimuli for investigating the learning of novel word-meaning pairs. *Behav Res Methods Instrum Comput*. 2004; 36:599–603. [PubMed: 15641405]
- Hengst J, Duff MC. Clinicians as communication partners: developing a mediated discourse elicitation protocol. *Top Lang Disord*. 2007; 27:37–49.
- Hengst J, Duff MC, Dettmer A. Rethinking repetition in therapy: repeated engagement as the social ground of learning. *Aphasiology*. 2010; 24:887–901.
- Hertzog C, Kramer AF, Wilson RS, Lindenberger U. Enrichment effects on adult cognitive development: can the functional capacity of older adults be preserved and enhanced? *Psychol Sci Public Interest*. 2008; 9:1–65.
- Hirono N, Mori E, Ikejiri Y, Imamura T, Shimomura T, Ikeda M, Yamashita H, Takatsuki Y, Tokimasa A, Yamadori A. Procedural memory in patients with mild Alzheimer's disease. *Dement Geriatr Cogn Disord*. 1997; 8:210–216. [PubMed: 9213065]
- Hodges JR, Patterson K. Is semantic memory consistently impaired early in the course of Alzheimer's disease? Neuroanatomical and diagnostic implications. *Neuropsychologia*. 1995; 33:441–459. [PubMed: 7617154]
- Hupet M, Chantraine Y, Nef F. References in conversation between young and old normal adults. *Psychol Aging*. 1993; 8:339–346. [PubMed: 8216954]
- Hyman BT, Van Hoesen GW, Damasio AR, Barnes CL. Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. *Science*. 1984; 225:1168–1170. [PubMed: 6474172]
- Hyman BT, Van Hoesen GW, Kromer LJ, Damasio AR. Perforant pathway changes and the memory impairment of Alzheimer's disease. *Ann Neurol*. 1986; 20:472–481. [PubMed: 3789663]
- Hyman BT, Van Hoesen GW, Damasio AR. Memory-related neural systems in Alzheimer's disease: an anatomic study. *Neurology*. 1990; 40:1721–1730. [PubMed: 2234428]
- Kukull WA, Larson EB, Teri L, Bowen J, McCormick W, Pfanschmidt ML. The Mini-Mental State Examination score and the clinical diagnosis of dementia. *J Clin Epidemiol*. 1994; 47:1061–1076. [PubMed: 7730909]
- McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984; 34:939–944. [PubMed: 6610841]

- McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7:263–269. [PubMed: 21514250]
- McKittrick LA, Camp CJ, Black FW. Prospective memory intervention in Alzheimer's disease. *J Gerontol*. 1992; 47:337–343.
- Molloy, DW.; Lubinski, R. Dementia: impact and clinical perspectives. In: Lubinski, R., editor. *Dementia and communication*. San Diego: Singular Publishing Group; 1997. p. 2-21.
- Morris JC. The clinical dementia rating (CDR): current version and scoring rules. *Neurology*. 1993; 43:2412–2414. [PubMed: 8232972]
- Nestor PJ, Fryer TD, Hodges JR. Declarative memory impairments in Alzheimer's disease and semantic dementia. *NeuroImage*. 2006; 30:1010–1020. [PubMed: 16300967]
- Nithianantharajah J, Hannan AJ. Enriched environments, experience-dependent plasticity and disorders of the nervous system. *Nat Rev Neurosci*. 2006; 7:697–709. [PubMed: 16924259]
- O'Kane G, Kensinger EA, Corkin S. Evidence for semantic learning in amnesia: a study with the amnesic patient H.M. *Hippocampus*. 2004; 14:417–425. [PubMed: 15224979]
- Orange JB, Colton-Hudson A. Enhancing communication in dementia of the Alzheimer's type. *Top Geriatr Rehab*. 1998; 14:56–75.
- Ramanathan, V. *Alzheimer's discourse: some sociolinguistic dimensions*. Mahwah, NJ: Lawrence Erlbaum Associates; 1997.
- Ripich DN, Ziol E, Lee MM. Longitudinal effects of communication training on caregivers of persons with Alzheimer's disease. *Clin Gerontol*. 1998; 19:37–55.
- Rosenbaum RS, Gilboa A, Levine B, Winocur G, Moscovitch M. Amnesia as an impairment of detail generation and binding: evidence from personal, fictional, and semantic narratives in K.C. *Neuropsychologia*. 2009; 47:2181–2187. [PubMed: 19100757]
- Salmon D, Butters N, Chan A. The deterioration of semantic memory in Alzheimer's disease. *Can J Exp Psychol*. 1999; 53:108–116. [PubMed: 10389493]
- Schmolck H, Kensinger E, Corkin S, Squire L. Semantic knowledge in patient H.M. and other patients with bilateral medial and lateral temporal lobe lesions. *Hippocampus*. 2002; 12:520–533. [PubMed: 12201637]
- Schuff N, Woerner N, Boreta L, Kornfield T, Shaw LM, Trojanowski JQ. Alzheimer's Disease Neuroimaging Initiative. MRI of hippocampal volume loss in early Alzheimer's disease in relation to ApoE genotype and biomarkers. *Brain*. 2009; 132(Pt 4):1067–1077. [PubMed: 19251758]
- Shune S, Duff MC. Verbal play as an interactional discourse resource in Alzheimer's disease. *Aphasiology*. 2012; 26:811–825. [PubMed: 23129879]
- Skotko B, Kensinger E, Locascio J, Einstein G, Rubin D, Tupler L, Krendl A, Corkin S. Puzzling thoughts for H.M.: can new semantic information be anchored to old semantic memories? *Neuropsychology*. 2004; 18:756–769. [PubMed: 15506844]
- Solomon JC. Humor and aging well: a laughing matter or a matter of laughing? *Am Behav Sci*. 1996; 39:249–271.
- Squire EJ, Hunkin NM, Parkin AJ. Errorless learning of novel associations in amnesia. *Neuropsychologia*. 1997; 35:1103–1111. [PubMed: 9256375]
- Stark SM, Stark CE, Gordon B. New semantic learning and generalization in an amnesic patient. *Neuropsychology*. 2005; 19:139–151. [PubMed: 15769198]
- Tennant KF. Laugh it off. The effect of humor on the well-being of the older adult. *J Gerontol Nurs*. 1990; 16:11–17. [PubMed: 2254592]
- Tse MMY, Lo APK, Cheng TLY, Chan EKK, Chan AHY, Chung HSW. Humor therapy: relieving chronic pain and enhancing happiness for older adults. *J Aging Res*. 2010 Epub ahead of print.
- Van Hoesen GW. Ventromedial temporal lobe anatomy, with comments on Alzheimer's disease and temporal injury. *J Neuropsychiatry Clin Neurosci*. 1997; 9:331–341. [PubMed: 9276838]

- Van Hoesen, GW.; Damasio, AR. Neural correlates of cognitive impairment in Alzheimer's disease. In: Plum, F., editor. Handbook of physiology: Section 1, Vol.V. The nervous system: higher functions of the brain. Baltimore: American Physiological Society; 1987. p. 871-898.
- Van Hoesen GW, Hyman BT, Damasio AR. Entorhinal cortex pathology in Alzheimer's disease. *Hippocampus*. 1991; 1:1–8. [PubMed: 1669339]
- van Praag, Kempermann, Gage. Neural consequences of environmental enrichment. *Nat Rev Neurosci*. 2000; 1:191–198. [PubMed: 11257907]
- Warrington EK, Weiskrantz L. Amnesic syndrome: consolidation or retrieval? *Nature*. 1970; 228:628–630. [PubMed: 4990853]
- Yorkston KM, Bourgeois MS, Baylor CR. Communication and aging. *Phys Med Rehab Clin N Am*. 2010; 21:309–319.

Figure 1.

Table set up for collaborative referencing task. Note: Each member of the pair has an identical board and set of cards. The cards on the Director's side (right) are in a predetermined location while the cards on the Matcher's side (left) are placed around the perimeter of the board at the start of each trial.

Figure 2.
The set of experimenter-generated alien-word pairs.

Figure 3.

AD Participants show intact rate of learning. **a, b:** Mean time (s) and mean word counts (number of words required for referencing the cards) for AD participants and their communication partners (black line) and for pairs of comparison participants (gray line) to complete placement of all 12 tangrams on each of the trials.

Figure 4.

Similar performance of AD and amnesia pairs. **a, b:** Mean time (s) and mean word counts (number of words required for referencing the cards) for AD participants and their communication partners (black line) and amnesic participants and their communication partners participants (gray line) to complete placement of all 12 tangrams on each of the trials.

TABLE 1

Demographic and Neuropsychological Data of Participants With Very Mild Alzheimer's Disease

	001AD	002AD	003AD	010AD	013AD
Age at testing	71	84	80	72	78
Education	12	12	16	20	14
CDR Score ¹	0.5	0.5	0.5	0.5	0.5
CVLT Delay ²	0	1	0	0	6
CFT Delay ³	7.5	4.5	8.5	2	3.5
COWA Test ⁴	35 (10)	32 (10)	35 (10)	30 (9)	33 (10)
Boston Naming Test ⁴	43 (5)	N/A	56 (13)	53 (10)	53 (10)
Animal Fluency Test ⁵	15	N/A	11	12	14
WAIS-III Digit Span Forward ⁶	6 (−0.10)	2 (0.88)	6 (0.09)	6 (−0.10)	5 (−0.84)
WAIS-III Digit Span Backward ⁶	6 (1.38)	5 (0.78)	2 (−2.18)	4 (−0.34)	3 (−1.12)
Trail Making Test Part A ⁷	33 (11)	65 (7)	48 (9)	30 (12)	38 (11)
Trail Making Test Part B ⁷	58 (13)	208 (7)	D/C (2)	122 (9)	119 (10)
WAIS Similarities Subtest ⁸	8	8	N/A	10	N/A
WAIS Block Design Subtest ⁸	15	10	16	10	8

AD = Alzheimer's disease; CVLT = California Verbal Learning Test; CFT = Complex Figure Test; COWA = The Controlled Oral Word Association test; WAIS = Wechsler Adult Intelligence Scale. Bolded scores are severely defective and/or are at least 2 SDs below the mean. N/A indicates that the participant did not complete the task during testing.

¹For the CDR scores, 0.5 = very mild dementia, 1 = mild dementia, and 2 = moderate dementia.

²The scores for the CVLT delayed test are raw scores out of 16 possible points.

³The scores for the CFT delayed test are raw scores out of 36 possible points.

⁴Scores for the COWA and Boston Naming Tests are raw scores with age-corrected scaled scores in parentheses.

⁵Animal Fluency Scores are raw scores.

⁶Scores for Digit Span Forward and Backward are numbers for the longest digit span the participant could repeat with Z-scores in parentheses.

⁷Trail Making Test A and B scores are in seconds with age-corrected scaled scores in parentheses.

⁸Scores for the Similarities and WAIS Block Design subtests are in age-corrected scaled scores.

TABLE 2

Description by an AD Participant and Partner on Trial 1 to Place First Card

You don't want to start with number one? No...**Alright, what do you want to start with, what number?** I- I want- I wanna uh tell you, what I think they look like and see if you agree ...**Alright...** Okay, uh- and- and...**We got the silo one...** Yes...**Yes...** And then the next one u- is the corn crib and a- a- like a tree beside it...**Wait a minute, corn crib, you mean does it have an arrow on top?** Yeah, it's- it's shootin' upward instead of down...**And it- does it have a- does it have a...** The barn. Corn crib...**Yes, the corn crib, and then it looks like an arrow** ...Yeah...**Yes...** Okay, now go to the left end of that...**But see mine are different than yours, so** ...No, they are- don't think so. Okay, I- I think some of these...3...I can see somebody like in a cap and gown...**I can too, one of them looks like they are praying...** Yes...**One of them looks like they're leaned over praying one looks like it's straight up praying...** Well, an- and one of e-e-s-s-sittin' with his...head over. He- he-...**Yes, his head over and feet out...** Okay...**I see that one...** Okay. **But now let's start with the...** W-...**Okay, and one looks like a dog, I see a couple that look like dogs...** Alrigh- ...**One has his mouth open** ...3... Okay ...with a- with a- with a diamond...on the top of a hump of the back...M hm...**Do you see that?** The diamond is a square? **I-it's a- it- it's diamond shape, and it sits...ab- on- it- almost on top of a ... triangle that comes up the middle of the dog's back. And the dog's mouth looks like it's open** ..2..**Do you not see that one?** Hm m...**Okay...What about a dog, with a ta::il, and two, one rectangle and one square on top of the back..2..and a rectangle...** First the rectangle, then a square...and the tail is a...triangle pointing downward..2..and it looks like a little

Scotty dog... Okay...he- he- he's runnin' and his back legs touchin' and his front legs are-...**Are out...** Uh huh...**And on top of his back is a rectangle...** And a square...and then on top of the rectangle is a square...M hm...and then the tail is going down- wards... Yeah, I- I- I see that one...**Yes. Then, there's...** Th- th then am I- I'm supposed to get m- I'm supposed to tell you-...**Where- ...What- what? What is on- don't, you're not supposed to touch yours...You're supposed to describe to me what is on your number one squa- number one...** Oh...**Which one?** ...Well I'd like to go backwards cause it's easier...**Starting at twelve?** For des- cry- yeah ...**Down at the bottom?** Uh- right... Bottom right. **Which one is yours? Which one is it on there?** Okay, it- it's the- the co- the corn crib-...**The corn crib?** ...with a silo goin' up to the right. **Okay, I'm gonna put that on number twelve.**

Bold text is familiar communication partner; ...3... Number of seconds of relative silence; ::: Indicates prolonged sound or syllable; ...Notes a pause in speech of less than one second, - Indicates cutoff of speech (either stuttering, or cut off by other person).

TABLE 3

Card Descriptions by the Same AD Participant and Partner on Trial 12

Card #	Card description
5	Pr- pr- prayer detached
12	Barking dog
1	Kicker
4	Sleeper
7	Pointy head
2	Blower
11	Uh, dog with two things on his back
9	Silo
8	Floating t- triangles
12	Uh what's that one called? Reading the book down low? Two mountains? N- the last one is a is a is a: s- uh Is the arrow? Arrow u- going up.
2	And then is there two mountains? Two mountains. Is eleven or ten? Eleven is two mountains.
6	Okay, and then other one.

Bold text is familiar communication partner.