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Dissociable Contributions of Amygdala and Hippocampus to Emotion and Memory in Patients with Alzheimer's Disease

Edmarie Guzmán-Vélez,[1,2,3] David E. Warren,[2,3] Justin S. Feinstein,[4,5] Joel Bruss,[2,3] and Daniel Tranel[1,2,3]*

ABSTRACT: The amygdala and the hippocampus are associated with emotional processing and declarative memory, respectively. Studies have shown that patients with bilateral hippocampal damage caused by anoxia/ischemia, and patients with probable Alzheimer's disease (AD), can experience emotions for prolonged periods of time, even when they cannot remember what caused the emotion in the first place (Feinstein et al. (2010) Proc Natl Acad Sci USA 107:7674-7679; Guzmán-Vélez et al. (2014) Cogn Behav Neurol 27:117-129). This study aimed to investigate, for the first time, the roles of the amygdala and hippocampus in the dissociation between feelings of emotion and declarative memory for emotion-inducing events in patients with AD. Individuals with probable AD ($N = 12$) and age-matched healthy comparisons participants (HCP; $N = 12$) completed a high-resolution (0.44 × 0.44 × 0.80 mm) T2-weighted structural MR scan of the medial temporal lobe. Each of these individuals also completed two separate emotion induction procedures (sadness and happiness) using film clips. We collected real-time emotion ratings at baseline and multiple times postinduction, and administered a test of declarative memory shortly after each induction. Consistent with previous research, hippocampal volume was significantly smaller in patients with AD compared with HCP, and was positively correlated with memory for the film clips. Sustained feelings of emotion and amygdala volume did not significantly differ between patients with AD and HCP. Follow-up analyses showed a significant negative correlation between amygdala volume and sustained sadness, and a significant positive correlation between amygdala volume and sustained happiness. Our findings suggest that the amygdala is important for regulating and sustaining an emotion independent of hippocampal function and declarative memory for the emotion-inducing event. © 2015 Wiley Periodicals, Inc.

KEY WORDS: declarative memory; MRI; dementia; MTL; emotion processing

[1] **Department of Psychological and Brain Sciences, University of Iowa;** [2] **Department of Neurology, University of Iowa College of Medicine, Iowa City, Iowa;** [3] **Division of Behavioral Neurology and Cognitive Neuroscience, University of Iowa College of Medicine, Iowa City, Iowa;** [4] **Laureate Institute for Brain Research, Tulsa, Oklahoma;** [5] **Department of Psychology and Faculty of Community Medicine, University of Tulsa, Oklahoma**

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*Correspondence to: Daniel Tranel, Department of Neurology, Division of Behavioral Neurology and Cognitive Neuroscience, University of Iowa College of Medicine, 200 Hawkins Drive, Iowa City, IA 52242. E-mail: daniel-tranel@uiowa.edu

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INTRODUCTION

A strong link between emotions and memory has been well established in the literature (LaBar and Cabeza, 2006). Studies have shown that healthy individuals and patients with Alzheimer's disease (AD) generally recall and recognize emotionally arousing stimuli better than emotionally neutral stimuli (Mori et al., 1999; Denburg et al., 2003; Fleming et al., 2003; Kumfor et al., 2014). This coupling between emotion and memory processes may be attributable to interaction of brain structures in the medial temporal lobe (MTL) including the amygdala and hippocampus, which are known to be important for emotion and declarative memory, respectively (Dolcos et al., 2004; Richardson et al., 2004).

Recent studies have reported a dissociation between emotions and memory for the emotion-inducing events. In one of these studies, we showed patients with AD and healthy comparison participants (HCP) a collection of film clips that induced feelings of either sadness or happiness (Guzmán-Vélez et al., 2014). Participants were asked to complete memory tests for the content of the films, and to rate their current emotional experience before the beginning of the films and at three different times after the end of the films. Patients with AD reported feeling "sad" or "happy" for up to 30 min even when they had very impaired memory for the films. We reported similar findings for amnesic patients with bilateral focal damage to the hippocampus (Feinstein et al., 2010). Similar to patients with AD, amnesic patients reported feeling sad or happy for a prolonged time but could not remember why (Feinstein et al., 2010).

While these behavioral findings were statistically robust, there was variability between participants in memory performance and degree of sustained emotion, which could potentially be informed by neuroanatomy. Patients with AD and HCP from our study had undergone a high-resolution structural MRI contemporaneous to the behavioral portion of the study. This provided a unique opportunity to examine the neural correlates of the dissociation between feelings of emotion and memory for the emotion-inducing event. Previous research has shown that damage to the hippocampus results in impaired declarative memory

(Scoville and Milner, 1957; Squire et al., 1992; Doxey and Kirwan, 2015; Eichenbaum and Cohen, 2014), whereas damage to the amygdala has been implicated in impaired emotional processing (Phelps and LeDoux, 2005; LeDoux, 2007), including recognition of facial emotion (Adolphs et al., 1999), experience of fear (Feinstein et al., 2011, Hamann, 2011), and emotional modulation of memory (Cahill et al., 1995; Adolphs et al., 2000).

Interestingly, the amnesic patients reported by Feinstein et al., (2010) had bilateral hippocampal lesions, and relatively intact amygdala volume. Similar to amnesic patients, patients with AD often have preserved emotional functions (and associated brain regions; Mori et al., 1999). Further, patients with AD typically manifest declarative memory impairment early in the development of the disease (Pantel et al., 2004; Jahn 2013), which is partly a product of the gradual neurodegeneration in the hippocampus (Hyman et al., 1984). However, changes in both hippocampal and amygdala volume vary with disease stage and between individuals.

Therefore, the dissociation between declarative memory and sustained emotion in patients with AD may be informed by characterization of amygdala and hippocampal volumes. We investigated such characterization by analyzing data collected from high-resolution images using MRI. We predicted that: (1) amygdala volume would be correlated with sustained emotion; and (2) hippocampal volume would be correlated with declarative memory for the emotion-inducing event.

MATERIALS AND METHODS

Participants

We tested patients with probable AD ($N = 17$) on a behavioral task as reported in our previous study (Guzmán-Vélez et al., 2014). A subset of these patients completed an MRI scan ($N = 12$; 9F, 3M). The remaining patients ($N = 5$) were not studied with MRI due to contraindications (e.g., claustrophobia, irremovable metals in the body), and are not described further. We recruited 9 patients from the Benton Neuropsychology Laboratory at the University of Iowa Hospitals and Clinics. These patients had been diagnosed under the auspices of the Department of Neurology at our institution, in the context of their medical and neuropsychological workup for dementia, following the McKhann et al. criteria (2011). We recruited 3 patients from the Alzheimer's Association. These patients had been diagnosed at an outside hospital by their primary care physician or neurologist. In the group of patients with probable AD, the mean age was 72.4 years (SD = 6.3, range = 60–79), and the mean level of education was 14.4 years (SD = 2.7, range = 8–18). The Clinical Dementia Rating (CDR; Morris, 1993) was used to measure the severity of AD, and this ranged from very mild (CDR of 0.05) to mild dementia (CDR of 1) in the AD group.

We also tested 12 HCPs (9F, 3M). Their mean age was 71.2 years (SD = 6.8, range = 60–80), and their mean educational attainment was 15.2 years (SD = 2.5, range = 12–18). Individuals in this group were recruited from the Cognitive Neuroscience Registry for Normative Data at the University of Iowa. There were no significant between-group differences in age, education, depression, or state anxiety (all P values > 0.05).

To determine eligibility for the AD group, we used interviews with the candidate patient and caregiver, neuropsychological measures, and medical records. For both the AD and HCP groups, we excluded individuals who had a neurological disorder (other than AD for the patient group), a psychiatric disorder (e.g., major depression or anxiety), uncorrected severe vision or hearing impairment, or a history of learning disability. We also excluded individuals who had impaired basic attention or visuospatial abilities or impaired comprehension, using standard neuropsychological data available for all participants.

Our study was approved by the University of Iowa Institutional Review Board. All participants gave their informed written consent or assent before beginning the study. We used previously standardized procedures (DeRenzo et al, 1998) to determine the patients' capacity to consent. When we determined that patients could not consent, their caregivers provided informed consent and the patients signed an assent document.

To clarify, the 12 patients with AD and the 12 HCPs were subsets from larger groups reported previously in the Guzmán-Vélez et al. (2014) study. Here, we focus on the structural MRI data (amygdala and hippocampal volumes, in particular), and how those data correlate with the behavioral (memory, emotion) data. We report the behavioral data here, for clarity and ease of exposition, with the understanding that these behavioral data were included in the previous study as part of larger groups.

Procedure

Participants underwent the procedure described in Guzmán-Vélez et al. (2014). Briefly, each emotion induction entailed watching a series of short emotionally evocative film clips (~18 min in total) aimed at inducing states of sadness or happiness. These film clips were chosen from sets of previously validated films shown to be highly effective at inducing emotion (Philippot, 1993; Gross and Levenson, 1995; Rottenberg et al., 2007; Schaefer et al., 2010). In the study by Guzmán-Vélez et al. (2014) patients with AD and HCPs reported increased levels of negative affect and decreased positive affect after the sadness films, and increased levels of positive affect and decreased negative affect after the happy films, evidencing the effectiveness of the films at inducing the targeted valence. Furthermore, participants in the current study reported a significant change from baseline in arousal after both the sad ($T(21) = 6.432$, $P < 0.0001$) and happy ($T(21) = 3.345$, $P = 0.0032$) films (there was missing data for 1 patient). All participants watched

the sadness inducing films first and happiness inducing films last in order to end sessions on a positive note.

Participants completed a free recall memory test 5 min after the end of the films during which they were asked to provide as many details as they could about each of the films. Further, participants rated how they felt "right now, in the present moment" immediately before the films (baseline), and multiple times after the end of the films including immediately after the end of the films (after induction), and 25–30 min after the end of the films (final rating). Participants rated how sad or happy they felt using 2 modified 100-point visual analog scales. These scales ranged from "I don't feel sad/happy at all" (0) to "I feel extremely sad/happy" (100).

To minimize demand characteristics during the experiment, we repeatedly reminded participants, "There are no right or wrong answers. We ask only that you answer as honestly as possible."

MR Data Acquisition

All participants underwent an MR scan no more than two weeks after completing the behavioral portion of the study. MR scans were completed at the Magnetic Resonance Research Facility (MRRF) at the University of Iowa using a Siemens TIM Trio 3T scanner. High-resolution T2-weighted imaging was applied to targeted regions in the MTL including amygdala and hippocampus, along with a lower resolution T2-weighted whole-brain localizer scan and a whole-brain T1-weighted scan (Warren et al., 2012). The whole-brain localizer was used to target the MTLs and define the orientation for the high-resolution scan, and had the following parameters: TE = 14 ms; TR = 6350 ms; FOV = 256 × 256 mm; Slice Thickness/Gap = 2.0/0.0 mm; Matrix = 256 × 256; Bandwidth = 315 Hz/Pixel; Turbo Factor = 9; duration = 3 m 37 s. The high-resolution T2-weighted scans were a 2D turbo spin-echo sequence with the following parameters: TE = 98 ms; TR = 9000 ms; FOV = 170 × 170 mm; Slice Thickness/Gap = 0.8/0.0 mm; Matrix = 384 × 308; Bandwidth = 246 Hz/Pixel; Turbo Factor = 17; Averages = 4. The high-resolution T2-weighted scan was repeated a total of three times, each lasting 15 min. Finally, a 5-min. whole-brain T1 MP-RAGE sequence was collected to provide further context for the high-resolution images (TE = 3.52 ms; TR = 2530 ms; TI = 1100 ms; FOV = 200 × 200 × 224 mm; Slice Thickness/Gap = 1.0/0.0 mm; Matrix = 256 × 256 × 224; Bandwidth = 190 Hz/Pixel). The MRI exam lasted 1 h.

Neuroimaging Data Processing

During image processing, the lower resolution T1 and T2 scans were submitted to the BRAINS automated preparation pipeline (Andreasen et al., 1996; Magnotta et al., 1999; Pierson et al., 2011) for image normalization and co-registration in stereotactic space (AC-PC aligned). Next, the three high-resolution T2-weighted MTL scans collected from each participant were coregistered and averaged to improve the signal-to-noise ratio. An image registration pipeline was implemented in BRAINS to align the scans in an orientation most suitable for accurate tracing of the anatomy of the hippocampus and amygdala (i.e., perpendicular to the long axis of the hippocampus). Finally, the averaged high-resolution volume was registered with the lower resolution images for comparison and additional neuroanatomical context.

Volumetric Data Analysis

Masks for the hippocampus and amygdala were manually traced on contiguous slices using the high-resolution data in Slicer3 and FSLView software. Images of MTL tissue captured in each volume were manually parcellated using existing tracing guidelines (Insausti et al., 1998; Nacewicz et al., 2006), and through consultation with atlases (Mai et al., 1997; Duvernoy, 2005) and neuroanatomical experts. All tracings were conducted by the first author and corroborated by the second author (DW). Tracings were not considered final until consensus was reached between both raters. Two automated methods (FreeSurfer and BRAINS) were used to corroborate outcomes from the manual ratings (see Results).

Raw volumes of the traced masks were then corrected for the well-characterized effects of age and sex using the method of Allen et al. (2005). Specifically, we used the age and sex of a given participant to calculate expected volumes of hippocampus and amygdala using the parameter weights provided by Allen et al. (2006). Then, we subtracted the predicted volume from the observed volume, creating a simple difference score, which was in turn divided by the standard error of the regression model fit by Allen et al. (2005), yielding a Studentized residual value. Finally, Studentized residual values obtained using this method were recentered on the mean value of the comparison participants in our sample.

In addition to the manual tracing of the higher resolution T2 scans, lower-resolution scans were submitted to two automated pipelines for tissue classification and anatomical parcellation. Variables of interest were normalized cerebrum volume (from BRAINS) for between-group comparisons; hippocampal volume (from BRAINS and Freesurfer) for comparison with manual volumetrics; and amygdala volume (from Freesurfer) for comparison with manual volumetrics. First, the low-resolution T1 and T2 scans were submitted to the BRAINS automated preparation pipeline. As described above, this pipeline was used to normalize and align these scans. Additionally, the BRAINS pipeline produced volumetric estimates for hippocampus, cortical gray matter, cortical white matter, and intracranial volume. The latter volumes were used to estimate the normalized volume of cerebrum, which we operationalized as summed cortical gray and white matter divided by intracranial volume. Second, the FreeSurfer pipeline was applied to each scan for additional automated segmentation and parcellation. FreeSurfer successfully parceled 19 of 24 T1 scans (NC, 10 of 12; AD, 9 of 12); the remaining T1 scans could not be processed by Freesurfer due to excessive motion, and data for those participants were excluded from Freesurfer-based analysis. All scans were successfully parceled by BRAINS, so analyses using BRAINS volumes retained all participants.

Statistical Analysis

Data were analyzed using R statistical package (R Project for Statistical Computing, http://www.r-project.org/). All tests used $\alpha = 0.05$.

A one-tailed paired two-sample t-test was used to evaluate between-group differences on a test of declarative memory (i.e., number of details recalled) given that patients with AD had impaired memory as measured by performance in neuropsychological tests and were therefore expected to do worse on a test of declarative memory. Sustained emotion was operationalized as emotion ratings at the final timepoint after viewing the film clips (final rating). Effect sizes were calculated using a variant of Cohen's *d* that adjusts for small sample sizes, d_{adj}.

Correlation coefficients (Pearson's *r*) were calculated to compare automated volumetric data generated by FreeSurfer and BRAINS with volumetric data generated by manual tracing.

Between-group comparisons of cerebrum volume, amygdala volume, and hippocampal volume were conducted using planned contrasts implemented as nonpaired, equal variance t-tests. Effect sizes were calculated using d_{adj}. Correlations between amygdala and hippocampal volumes were characterized with Pearson's *r*.

Relationships between volumetric measures (hippocampus, amygdala, cerebrum) and behavioral results (recall or sustained emotion) were evaluated using linear regression. Behavioral results were considered first overall (i.e., across sad and happy conditions) and then separately for the two conditions. The outcome variable was behavior, and predictor variables were group membership (binary) and volume (continuous). Volume was centered on the HCP group mean before models were fitted. For each combination of volume and behavior, 5 regression models were fitted:

Null model	Behavior = intercept + error
Group model	Behavior = intercept + Group + error
Volume model	Behavior = intercept + Structural Volume + error
Group + Volume model	Behavior = intercept + Structural Volume + Group + error
Group × Volume model	Behavior = intercept + Structural Volume × Group + error

The best-fitting model for each relationship was determined by identifying the model with the smallest AIC value. Models with similar AIC values were directly compared using a Chi-squared test: if a better model with more terms provided a statistically significant improvement in fit, it was selected; if there was not a statistically significant difference, the model with fewer terms was preferred. Each section of the results describes the best-fitting model, while an omnibus summary including parameter values and inferential statistics is presented in Table 1.

RESULTS

Between-Group Behavioral Comparisons

Memory

As reported in Guzmán-Vélez et al. (2014), the AD group recalled significantly fewer details of both films overall than the HCP group, $T(22) = 6.064$, $P < 0.001$, $d_{adj} = 2.390$. This reduction in recall for the AD group was present for both the sad films, $T(22) = 4.341$, $P < 0.001$, $d_{adj} = 1.711$, and for the happy films, $T(22) = 6.708$, $P < 0.0001$, $d_{adj} = 2.644$.

Emotion

As shown in Figure 1, patients with AD and the HCP group reported feeling sad or happy for up to 30 min after the end of the film clips. Ratings for sad and happy films did not significantly differ between groups (each $T(22) < 1$, each $P > 0.30$, each $d_{adj} < 0.5$). Reports of happiness by both groups at the final rating were close to baseline, whereas participants reported high levels of sadness 30 min after the end of the films.

Volumetric Comparisons: Automated vs. Manual

Automated vs. manually parceled hippocampus

We employed a manual tracing method based on established tracing techniques and high resolution images of neuroanatomy with the strong expectation of providing very accurate estimates of structural volumes for hippocampus and amygdala. To corroborate these volumetric estimates, we compared our observed volumes to those produced by two automated methods (FreeSurfer and BRAINS). Raw manually traced hippocampal volume and FreeSurfer hippocampal volume were significantly and positively correlated overall ($r = 0.863$, $T(17) = 7.034$, $P < 0.001$) and for the AD and NC groups alone (each $r > 0.80$, each $T > 3.80$, each $P < 0.005$). Similarly, manually traced hippocampal volume and BRAINS hippocampal volume were significantly and positively correlated overall ($r = 0.456$, $T(22) = 2.406$, $P = 0.025$). Notably, this correlation was numerically larger (but of only marginal statistical significance) for the NC group ($r = 0.557$, $T(10) = 2.121$, $P = 0.060$) and numerically reduced for the AD group ($r = 0.368$, $T(10) = 1.252$, $P = 0.239$). This pattern may reflect the additional

TABLE 1.

Summary of Regression Analysis

Behavior	Structure	Emotion	Best-fit model	*F*	df	*P*	Adj. R^2	Intercept		Group		Volume		Grp × Vol	
								β	*P*	*β*	*P*	*β*	*p*	*β*	*p*
Recall	**Hippocampus**	**Overall**	Additive	25.870	2,21	<0.001	0.684	46.250	<0.001	−27.973	<0.001	**5.515**	**0.021**	–	–
		Sad	Additive	13.260	2,21	<0.001	0.516	25.417	<0.001	−13.335	0.002	**3.388**	**0.044**	–	–
		Happy	Additive	27.750	2,21	<0.001	0.699	20.833	<0.001	−14.639	<0.001	**2.127**	**0.055**	–	–
	Amygdala	**Overall**	Group	36.770	1,22	<0.001	0.609	46.250	<0.001	−32.583	<0.001	–	–	–	–
		Sad	Group	18.840	1,22	<0.001	0.437	25.417	<0.001	−16.167	<0.001	–	–	–	–
		Happy	Group	45.000	1,22	<0.001	0.657	20.833	<0.001	−16.417	<0.001	–	–	–	–
	Cerebrum	**Overall**	Group	36.770	1,22	<0.001	0.609	46.250	<0.001	−32.583	<0.001	–	–	–	–
		Sad	Group	18.840	1,22	<0.001	0.437	25.417	<0.001	−16.167	<0.001	–	–	–	–
		Happy	Additive	35.810	2,21	<0.001	0.752	20.833	<0.001	−13.414	<0.001	**3.426**	**0.006**	–	–
Sustained Emotion	**Hippocampus**	**Overall**	Null	–	–	–	–	13.324	0.009	–	–	–	–	–	–
		Sad	Null	–	–	–	–	22.833	<0.001	–	–	–	–	–	–
		Happy	Null	–	–	–	–	2.941	0.727	–	–	–	–	–	–
	Amygdala	**Overall**	Null	–	–	–	–	13.324	0.009	–	–	–	–	–	–
		Sad	Volume	7.060	1,22	0.014	0.209	22.801	<0.001	–	–	**−14.627**	**0.014**	–	–
		Happy	Volume	4.599	1,15	0.049	0.184	3.796	0.619	–	–	**20.481**	**0.049**	–	–
	Cerebrum	**Overall**	Null	–	–	–	–	13.324	0.009	–	–	–	–	–	–
		Sad	Null	–	–	–	–	22.833	<0.001	–	–	–	–	–	–
		Happy	Null	–	–	–	–	2.941	0.727	–	–	–	–	–	–

Summary of the best-fit models for regression of behavioral measures (recall and sustained emotion) onto normalized structural volumes (of hippocampus, amygdala, and cerebrum). Models were fit to both **overall** datasets that combined data from the sad and happy emotion conditions and to individual **sad** and **happy** condition data. Summary statistics and parameter values are presented for the best-fit model for each dataset. Briefly, the **null** model contained only an intercept term; the **group** model added a group factor; the **volume** model added a continuous volume predictor; and the **additive** model included both a group factor and the continuous volume predictor. An **interaction** model that included an interaction term between the group and volume factors was also tested but never provided the best fit. For recall data, group membership (HCP >AD) and hippocampal volume (positively related to recall) were significant predictors, while amygdala volume was not. Cerebrum volume was not a significant predictor of recall except for happy films, but that effect was subordinate to the influence of hippocampal volume (see Results). For sustained emotion data, none of group membership, hippocampal volume, nor cerebrum volume were significant predictors, but amygdala volume was related to sustained sad and happy emotion in opposite directions.

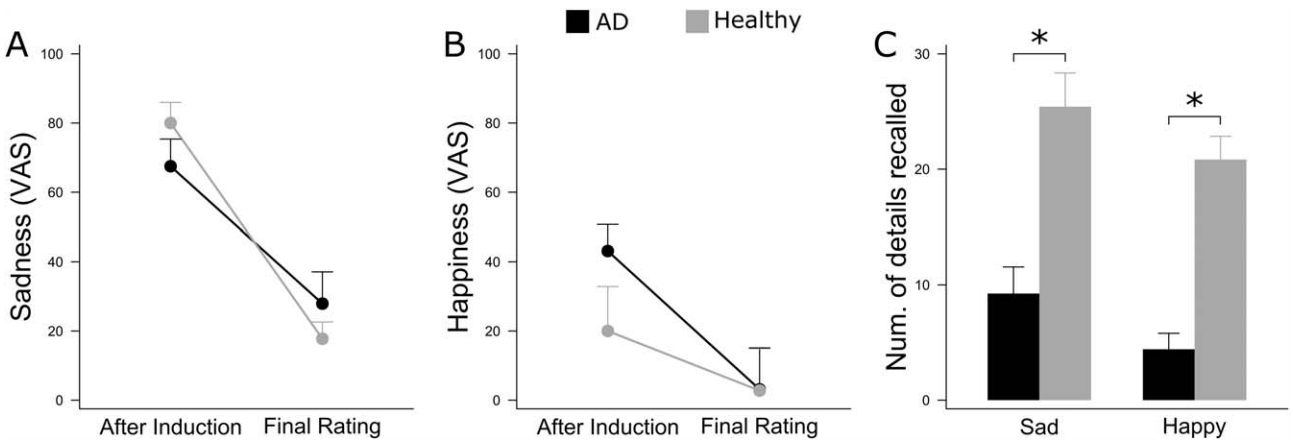

FIGURE 1. Behavioral results. Overall, the AD and HCP groups showed similar emotion induction and sustainment, but the AD group had significantly reduced memory. A: Both groups showed significant increases in sadness ratings immediately after the induction followed by some attenuation of sadness ratings after a 30-min. interval. B: A qualitatively similar pattern was observed for the happiness condition. C: For both sad and happy films, the HCP group recalled significantly more details than the AD group. Error bars show standard error of the mean.

challenges of successfully identifying the potentially atrophied hippocampus of AD patients using automated methods.

Automated vs. manually parceled amygdala

Volumetric estimates of amygdala were produced manually and using FreeSurfer (BRAINS did not provide amygdala volumes). Unlike manual and automated hippocampal volumes, these amygdala volumes were not significantly correlated overall ($r = 0.360$, $T(17) = 1.591$, $P = 0.130$) and differed for the AD and NC groups alone (AD, $r = 0.907$, $T(7) = 5.709$, $P < 0.001$; NC, $r = -0.383$, $T(8) = 1.172$, $P = 0.275$). This difference between manual and automated tracing for amygdala is not unprecedented because the amygdala is notoriously difficult to identify even for sophisticated software (Entis et al., 2012). Manual tracing of this structure remains the field's gold standard method (Entis et al., 2012), and our observations are consistent with this approach.

Between-Group Comparison of MTL Structure Volumes

The AD group had smaller hippocampal volumes than the HCP group, but amygdala volumes did not differ between the two groups. Specifically, hippocampal volume was significantly smaller in the AD group, $T(22) = 1.794$, $P = 0.043$, $d_{adj} = 0.707$, while amygdala volume was not different between the two groups, $T(22) = 0.012$, $P = 0.495$, $d_{adj} = 0.005$. Notably, volumes of the hippocampus and the amygdala were not significantly related to one another overall, Pearson's $r = 0.342$, $T(22) = 1.709$, $P = 0.102$ or within the comparison group alone, Pearson's $r = -0.163$, $T(10) = 0.524$, $P = 0.612$. However, hippocampal and amygdala volumes were significantly positively correlated within the AD group alone, Pearson's $r = 0.597$, $T(10) = 2.352$, $P = 0.041$. This relationship could potentially be attributable to a shared mechanism of MTL structure damage or atrophy in AD, although the lack of a significant group difference in amygdala volume in our sample is not entirely consistent with this explanation (Fig. 3).

Between-Group Comparison of Cerebrum Volume

Normalized volume of the cerebrum based on BRAINS parcellation was smaller in the AD group than the HCP group (see Fig. 3). The implied difference in raw volume was numerically modest ($\Delta = 45.950$ mm^3) but suggested that the cerebrum of the AD group may have been somewhat atrophied relative to the HCP group. This group difference in cerebrum volume may have been concentrated in white matter ($T(22) = 2.151$, $P = 0.043$, $d_{adj} = 0.848$) and attenuated in gray matter ($T(22) = 1.639$, $P = 0.115$, $d_{adj} = 0.646$), but the most statistically robust finding was for a difference in the combined volumes of gray matter and white matter ($T(22) = 2.205$, $P = 0.038$, $d_{adj} = 0.869$).

Relationships between Volumetric Measures and Behavior

Overview

This section describes the results of regression analysis of relationships between behavioral outcomes, volumetric measures, and group membership (see Methods). Full statistical details are provided in Table 1, and illustrations of the patterns associated with hippocampus and amygdala volumes are presented in Figures 4 and 5 (cerebrum volume is not depicted).

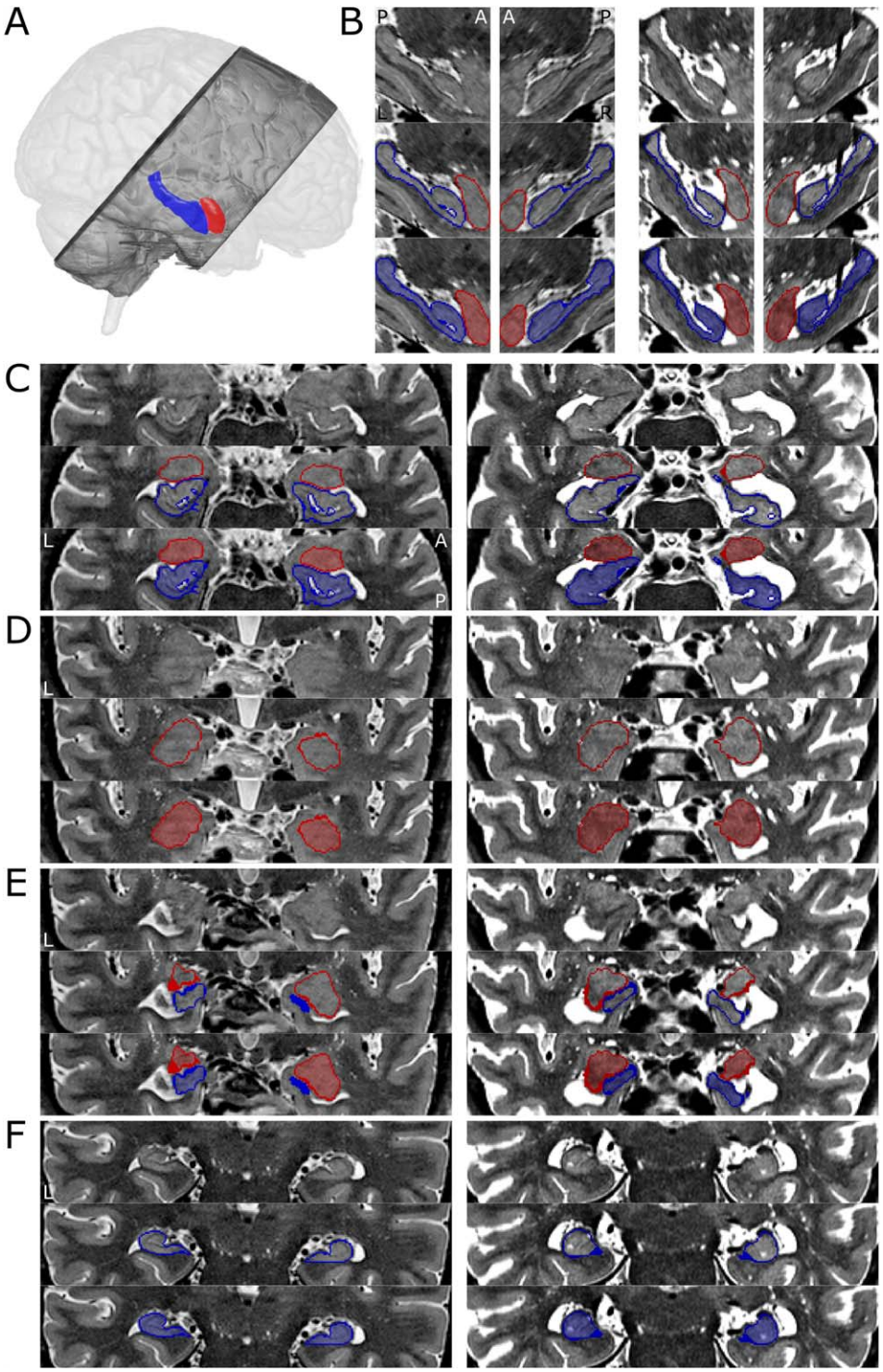

FIGURE 2. Neuroanatomical approach and representative sample images. A: High-resolution whole-brain images (translucent image) were complemented by a very high-resolution slab targeting the MTLs. These very high-resolution images were used to trace the hippocampus (blue) and amygdala (red). B: Sagittal sections from a HCP (left two columns) and an AD patient (right two columns). Top to bottom: raw image; outlines of hippocampus (blue) and amygdala (red) masks; and complete masks. C: Axial sections from the level of the optic chiasm. Left, healthy comparison; right, AD patient. D, E, and F: Coronal sections proceeding from anterior to posterior illustrating the amygdala (D), amygdala-hippocampus interface (E), and hippocampal body (F). Across all images, note the increased size of the lateral ventricles in the AD patient, as well as the atrophy of the hippocampus.

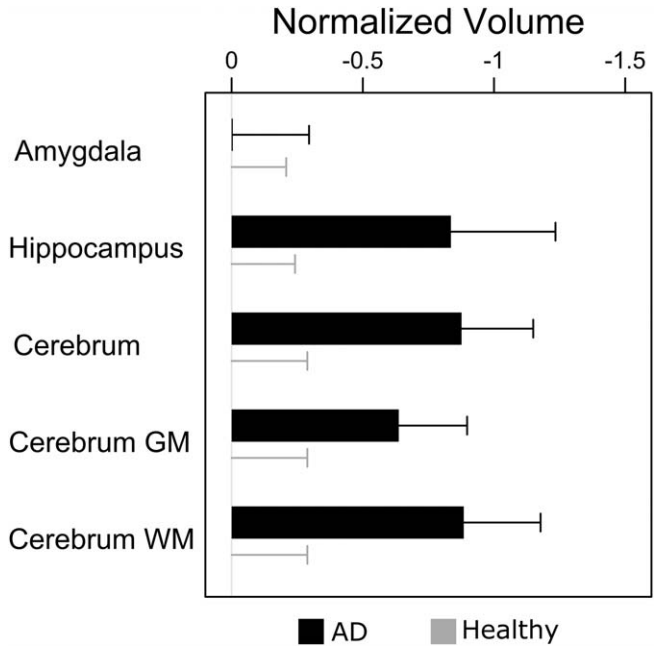

FIGURE 3. Group averages for the normalized volume of amygdala, hippocampus, and cerebrum. Structural volumes were mean-centered relative to the comparison group (mean-centering produced values of zero). A mean value of zero represents a lack of difference from normal volume. The AD group had amygdala volumes that did not differ from those of the HCP group; by contrast, hippocampal and cerebrum volumes were significantly reduced in the AD group. Error bars show standard error of the mean.

Memory

We observed a significant positive relationship between hippocampal volume and recall performance that did not differ by group. We did not observe any significant relationship between amygdala volume and recall performance. Qualitative patterns of these associations were similar for overall recall summed across emotion conditions and for individual emotion conditions.

Hippocampal volume

For overall recall memory, there were significant main effects of group and hippocampal volume as shown by the best-fitting model (Group + Volume model, see Methods: Statistical Analysis). As expected based on the analysis of behavioral results, the AD group had impaired recall relative to the HCP group. Additionally, there was a positive relationship between hippocampal volume and recall for both groups. The same qualitative pattern was observed for separate regression analyses of recall for sad film clips and happy film clips, both of which were also best fit by the Group + Volume model.

We followed up on the planned analysis of hippocampal volume and memory by examining the performance of AD participants who had no (zero) recall ($N = 3$) relative to the other AD participants (who were impaired but above zero). Consistent with the pattern described above, the mean standardized hippocampal volume of AD participants with no recall was numerically less than that of AD participants with some recall (−1.177 vs. −0.722).

Amygdala volume

Unlike hippocampal volume, amygdala volume was not statistically related to recall performance, as shown by the exclusion of amygdala volume from the best-fitting model (Group model, see Methods: Statistical Analysis). As before, the AD group had impaired recall relative to the HCP group, but there was no significant relationship between amygdala volume and

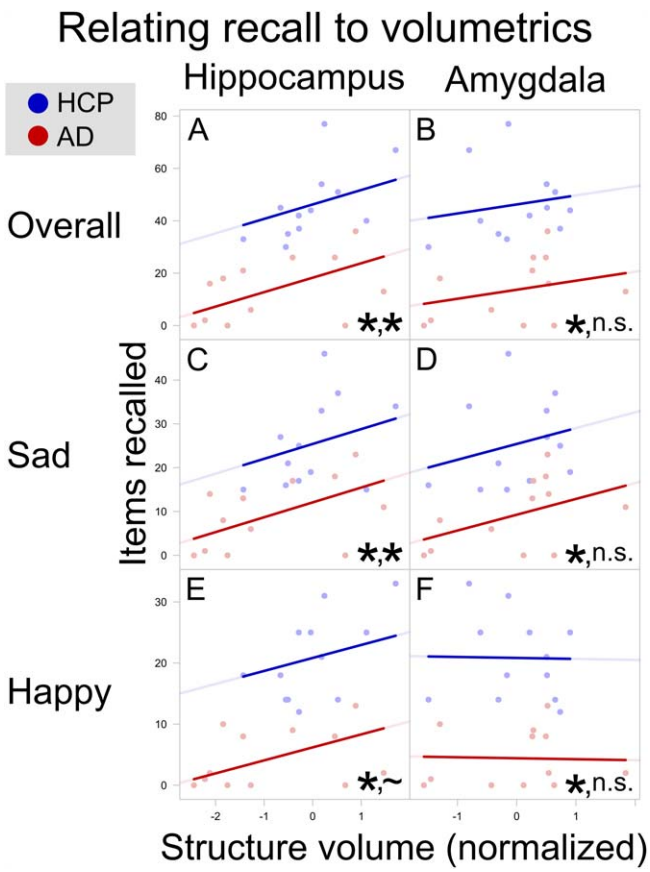

FIGURE 4. Item recall regressed on structural volume showed an influence of hippocampal volume (left column) but not amygdala volume (right column). The HCP group (blue points and lines) recalled more items than the AD group (red points and lines) in each condition. In addition, both groups showed a significant positive relationship between hippocampal volume and item recall overall and in the sad emotion condition; the happy emotion condition showed a qualitatively similar pattern but was only marginally significant. Meanwhile, amygdala volume was not significantly related to item recall overall or in either emotion condition (n.b. the apparent positive relationship for sad items was not significant). Statistical significance of model terms is indicated with two symbols: the first symbol indicates significance of the group term; the second symbol indicates significance of the volume term. Symbols: *, $P < 0.05$; ~, $P < 0.10$; n.s., $P > 0.10$ (see Table 1 for exact P values).

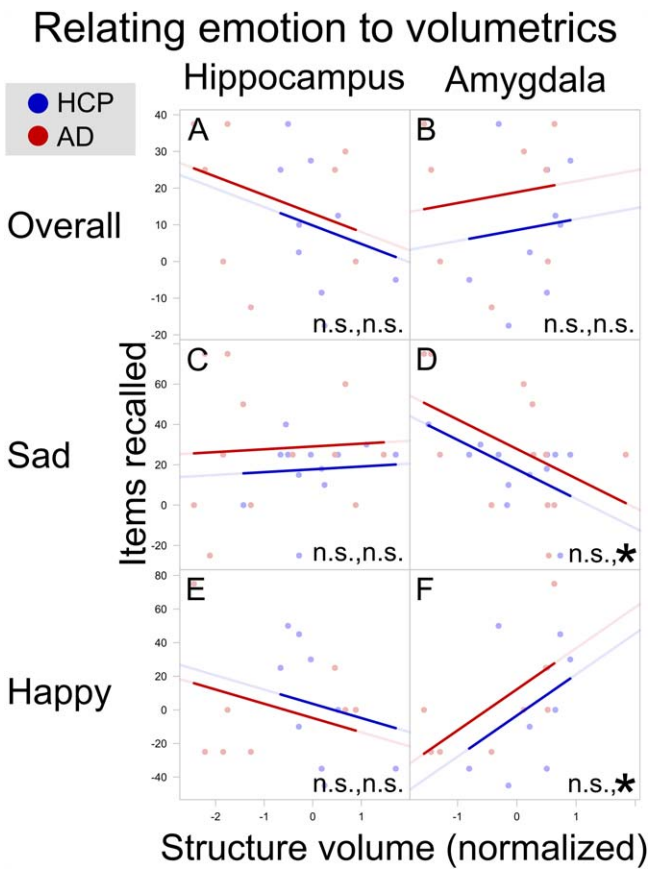

FIGURE 5. A measure of sustained emotion (see Methods) regressed on structural volume showed no significant influence of hippocampal volume (left column) and a complex influence of amygdala volume (right column). The HCP group (blue points and lines) and the AD group (red points and lines) had similar sustained emotion in all conditions. Unlike item recall (see Fig. 4), hippocampal volume was not related to sustained emotion. Meanwhile, amygdala volume was not significantly related to overall sustained emotion averaged across the two conditions, but in the two emotion conditions separately, there was evidence of a relationship. For the sad condition, increased amygdala volume was related to less sustained emotion, while for the happy condition increased amygdala volume was related to more sustained emotion. These significant and opposite patterns suggest a complex relationship between amygdala volume and sustained emotion (see Discussion). See Figure 4 caption for symbol information.

recall. The same qualitative pattern was observed for separate regression analyses of recall for sad film clips and happy film clips, both of which were also best fit by the Group model.

Cerebrum volume

Cerebrum volume was not statistically related to overall recall memory performance as shown by the exclusion of cerebrum volume from the best-fitting model (Group model). Again, the AD group had impaired recall relative to the HCP group, but there was no significant relationship between cerebrum volume and recall. This same pattern was found for recall of details for sad film clips. For recall of details from happy film clips the Group+Volume model was the best fit, indicating a positive relationship between cerebrum volume and recall performance.

Follow-up test

Our findings indicated that hippocampal volume and cerebrum volume were both positively related to recall of details from happy film clips. We tested whether the contributions of these two volumetric measures were unique by fitting a model that included Group, Hippocampal Volume, and Cerebrum Volume as predictor variables for the Recall outcome variable. In this model, we observed that Group and Hippocampal Volume were both significantly and positively related to recall while Cerebrum Volume was no longer significant. This non-significance of the Cerebrum Volume predictor suggested that it was redundant in the presence of superior predictor variables (Hippocampal Volume and Group).

Emotion

We observed no significant association of hippocampal volume or amygdala volume with overall sustained emotion. There was evidence of significant but opposite associations of amygdala volume with sustained emotion for sadness (negative) and happiness (positive). Regression analyses did not show a significant relationship between hippocampal volume and sadness or happiness.

Hippocampal volume

There was no statistical evidence for a correlation between hippocampal volume and sustained emotion, and no evidence that group membership affected sustained emotion. The null model was the best fit for overall sustained emotion and for each emotion condition.

Amygdala volume

There was no statistical evidence for an effect of amygdala volume or group membership on overall sustained emotion and as before, group membership was not related to sustained emotion in either emotion condition. However, there was evidence of an opposite-direction correlation of amygdala volume with sustained feelings of sadness or happiness. Specifically, amygdala volume was positively related to sustained happy emotion, but negatively related to sustained sad emotion. These intriguing findings are considered at greater length in the Discussion.

Cerebrum volume

There were no significant relationships between cerebrum volume and any measure of sustained emotion. The null model was the best fit in each condition.

DISCUSSION

We examined contributions of the amygdala and hippocampus to the dissociation between emotions and declarative memory in patients with probable AD and a group of HCP. Specifically, we tested the association between hippocampal volume and declarative memory for an emotionally salient event, and the association between amygdala volume and sustained emotion induced by the event. Patients with probable AD (as reported in the study by Guzmán-Vélez et al., 2014) displayed impaired declarative memory for the emotion-inducing films. Participants in the AD and HCP groups reported feeling sad or happy for up to 30 min after the end of the films. Both groups showed similar persistence of emotions regardless of memory for the emotion-inducing event.

Given that there were no differences between groups in sustained emotion, we predicted that amygdala volume would be comparable between groups. The results supported this prediction: patients with AD and HCP had similar amygdala volume on average. Follow-up analyses of amygdala volume revealed that amygdala volume was associated with sustained emotion. However, the pattern of this association differed for the two emotion types. Specifically, amygdala volume was positively associated with sustained happiness but negatively associated with sustained sadness. That is, those with larger amygdala volume reported a greater difference from baseline in the final happiness ratings yet a smaller difference from baseline in the final sadness ratings, and these effects did not differ between groups. These intriguing findings can be taken to suggest that those individuals with smaller amygdala volume were having more difficulty regulating negative emotions. In this vein, studies with diverse populations have reported a relationship between smaller amygdala volume and emotional dysregulation. For instance, smaller amygdala volume has been associated with increased anxiety in individuals with autism (Corbett et al., 2009), and with more pronounced symptoms of dysphoria and anxiety (among others) in patients with epilepsy (Tebartz van Elst et al., 2009). Along the same lines, it has been shown that individuals with larger gray matter volume in the amygdala report a higher ability to regulate emotions (Song et al., 2015). Thus, it is possible that those individuals with larger amygdala volume were able to regulate their negative emotions more effectively and therefore able to return to baseline faster.

Consistent with our predictions, we found significant differences in hippocampal volume between groups, with patients with probable AD having smaller hippocampal volume on average than HCP. As expected, we found a positive association between the volume of the hippocampus and declarative memory for the films. Notably, this positive association was observed in both the HCP and AD groups despite a general reduction in hippocampal volume for the AD group. There is extensive literature showing a relationship between hippocampal atrophy and memory impairment in patients with AD, such that individuals with smaller hippocampus perform worse in memory tests (Deweer et al., 1995; Kohler et al., 1998). The association between hippocampal volume and performance on tasks of declarative memory in healthy individuals is more mixed—some studies have reported a positive correlation between hippocampal volume and performance in memory tests, whereas others have failed to find an association (de Toledo-Morrell et al., 2000; Pohlack et al., 2014). Our findings suggest that hippocampal volume is positively associated with declarative memory in healthy older adults as well as in patients with AD, and support previous research demonstrating the important role of the hippocampus for declarative memory (Scoville and Milner, 1957; Squire et al., 1992; Doxey and Kirwan, 2015; Eichenbaum and Cohen, 2014).

A strength of our study lies in the manual tracing of high-resolution images of regions of the MTL, specifically of the amygdala and the hippocampus. Both structures have complex shapes that can be difficult for automated methods to identify reliably, and most automated methods are based on analysis of standard-resolution MRI images (e.g., 1 mm isotropic; Pantel et al., 2000; Morey et al., 2009; Shen et al., 2010). Although automated methods for hippocampal parcellation based on high-resolution images are improving, the best results are typically achieved by initially seeding the automated analysis with manual parcellation of several members of a target cohort collected on a particular MR scanner (Yushkevich et al., 2015). Therefore, for studies using small to moderate sample sizes, manual parcellation of locally collected data is likely to remain the gold standard. A future goal for this line of investigation will be direct comparison of hippocampal and amygdala volumes in older adults and AD patients derived using manual parcellation, unsupervised automated parcellation methods such as Freesurfer 5.3.0 package (http://surfer.nmr.mgh.harvard.edu/), and supervised parcellation methods (Yushkevich et al., 2015).

To verify that the correlations between brain structures and behavioral measures were not spurious, we examined the association of these behavioral measures with the cerebrum. Indeed, we did not find a significant association between the cerebrum and overall recall or sustained emotion, validating the specificity of our findings showing an association between hippocampal volume and declarative memory, and amygdala volume and sustained emotion.

Our study had several limitations. First, our sample size was modest. However, our high-resolution structural images allowed us to obtain more accurate measures of amygdala and hippocampal volumes compared with previous reports (e.g., Allen et al., 2005, 2006) that relied on images of lower resolution that revealed less anatomical detail. Notably, there was a strong association between hippocampal volumes generated by manual tracings and volumes generated by an automated method (Freesurfer). This is consistent with previous studies reporting that Freesurfer can reliably estimate hippocampal volume (Cherbuin et al., 2009). Nonetheless, amygdala volumes reported by Freesurfer were significantly different from those generated by manual tracing. The discrepancy between methods for amygdala volume has been reported in the past (Entis et al., 2012) and manual tracing remains the gold standard.

The quality of our very high-resolution images increases our confidence of having reliably identified the boundaries of this structure. Another limitation of our study is that we only collected structural MRI data. It will be important for future research to employ functional neuroimaging and other structural measures (e.g., diffusion-weighted imaging) that can contribute to our understating of the neural correlates of the dissociation between emotion and declarative memory.

In conclusion, our findings support previous research showing an important role of the hippocampus in declarative memory, and of the amygdala in emotional processing. Notably, these results improve understanding of MTL contributions to emotion and memory by suggesting that the amygdala is important for regulating and sustaining an emotion independent of both hippocampal volume and declarative memory. Furthermore, our high-resolution images of MTL structures allowed us to obtain accurate measures of amygdala and hippocampal volumes, and presumably, more precise estimates of the association of these structures with behavioral data. Finally, our findings emphasize the importance of treating patients with AD with respect and dignity. Although patients with AD might be unable to identify the source of their feelings, these feelings can linger for a prolonged period of time and impact their well-being. Furthermore, it is possible that patients with AD might experience negative affect for longer than expected in part because they have difficulty effectively regulating their emotions. In some cases, brain structures important for down-regulating negative emotion may be adversely affected by the disease. It is critical that caregivers, family members, and others who interact with patients with AD make significant efforts to improve patients' emotional well-being, even if the patients cannot recall the events that prompted their feelings in the first place.

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