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Disruption of amygdala-entorhinal-hippocampal network in late-life depression

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Abstract

Episodic memory deficits are evident in late-life depression (LLD) and are associated with subtle synaptic and neurochemical changes in the medial temporal lobes (MTL). However, the particular mechanisms by which memory impairment occurs in LLD are currently unknown. We tested older adults with (DS+) and without (DS-) depressive symptoms using high-resolution fMRI that is capable of discerning signals in hippocampal subfields and amygdala nuclei. Scanning was conducted during performance of an emotional discrimination task used previously to examine the relationship between depressive symptoms and amygdala-mediated emotional modulation of hippocampal pattern separation in young adults. We found that hippocampal dentate gyrus (DG)/CA3 activity was reduced during correct discrimination of negative stimuli and increased during correct discrimination of neutral items in DS+ compared to DS- adults. The extent of the latter increase was correlated with symptom severity. Furthermore, DG/CA3 and basolateral amygdala (BLA) activity predicted discrimination performance on negative trials, a relationship that depended on symptom severity. The impact of the BLA on depressive symptom severity was mediated by the DG/CA3 during discrimination of neutral items, and by the lateral entorhinal cortex (LEC) during false recognition of positive items. These results shed light on a novel mechanistic account for amygdala-hippocampal network changes and concurrent alterations in emotional episodic memory in LLD. The BLA-LEC-DG/CA3 network, which comprises a key pathway by which emotion modulates memory, is specifically implicated in LLD.

Keywords

memory; aging; emotion; pattern separation; hippocampus

Introduction

Late-life depression (LLD), or major depression occurring in older adults after the age 60–65 (Butters et al., 2008), is estimated to affect 15% of the elderly population (Gottfries,

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2001). LLD has serious consequences, including patient and caregiver distress and increased mortality due to high suicide rates in the elderly (Reynolds and Kupfer, 1999). There is no single agreed upon definition of LLD, however, many have suggested that it typically involves a depressive syndrome without sadness, or a depletion syndrome with withdrawal, apathy, and lack of vigor as the major symptoms (Blazer, 2003).

Episodic memory impairment is one of the most significant cognitive symptoms in LLD (Zakzanis et al., 1998; Elderkin Thompson et al., 2007), which is associated with alterations in hippocampal (Steffens et al., 2000; Lloyd et al., 2004; O'Brien et al., 2004; Hickie et al., 2005), entorhinal cortex (Bell-McGinty et al., 2002), and amygdala (Burke et al., 2011) volumes. Up to 50% of individuals with mild cognitive impairment (MCI) or Alzheimer's disease (AD) exhibit comorbid depressive symptoms (Lopez et al., 2005), and LLD is associated with an increased risk for dementia (Diniz et al., 2013).

Medial temporal lobe (MTL) changes in aging and depression have also been linked to alterations in pattern separation, the process of disambiguating similar events, which is thought to rely on the hippocampal dentate gyrus (DG) (Marr, 1971; Treves and Rolls, 1992; McClelland et al., 1995). Mnemonic discrimination tasks are modified recognition tests that are designed to assess hippocampal pattern separation by having to overcome interference among similar stimuli in memory. Prior work has shown impairment in mnemonic discrimination in young adults with depression (Shelton and Kirwan, 2013; Leal and Yassa, 2014) and in aging (Toner et al., 2009; Stark et al., 2010; Reagh et al., 2014a, 2016). While both aging and depression are associated with episodic memory deficits, not all types of information may be subject to loss and forgetting.

Memory for emotional experiences seems to be relatively well preserved with age (Kensinger et al., 2002; Denburg et al., 2003), some suggesting a "positivity effect" with age (Mather and Carstensen, 2005; Leal et al., 2016a). In depression, a negativity bias exists such that negative information tends to be better remembered than positive or neutral information (Watkins et al., 1996, 2000; Hasler et al., 2004; Gordon et al., 2008; Haas and Canli, 2008). We have developed an emotional discrimination task (Fig 1A) that allows us to assess pattern separation among highly similar emotional and non-emotional scenes. In older adults, we find preserved emotional relative to neutral discrimination compared to young adults who display the opposite (better neutral relative to emotional discrimination) (Leal and Yassa, 2014). In young adults with depressive symptoms, reduced neutral discrimination and enhanced negative discrimination has been observed (Leal et al., 2014b). This was further associated with a shift in MTL dynamics during negative discrimination characterized by a hyperactive amygdala and a hypoactive hippocampal DG/CA3 (Leal et al., 2014a). More recently, we have found that older adults with greater memory impairment show impaired BLA—LEC—DG/CA3 connectivity during negative discrimination and increased amygdala-hippocampal connectivity during negative false recognition (Leal et al., 2016b).

Given our prior work with this task, as well as the extant literature on MTL subregions impacted by depression and aging, we focused our regional analyses (Fig 1B) on the hippocampal DG/CA3, the basolateral amygdala (BLA), and the lateral entorhinal cortex

(LEC), as these regions form a distinct emotional memory processing circuit in the brain. We expect that while it is unlikely that late-life depression will be easily characterized as the linear sum of the effects previously noted in aging and depression independently, it is likely to involve the same MTL network. We planned to examine activity in these regions during accurate discrimination and false recognition during emotional versus neutral memory processing. We hypothesized that there would be a shift in DG/CA3 and BLA activity during negative discrimination in older adults with depressive symptoms (DS+) compared to those without depressive symptoms (DS-). More specifically, DS+ may show evidence of reduced DG/CA3 activity during negative discrimination (similar to previous findings in young adults with depressive symptoms) and may show altered LEC activity during emotional versus neutral memory processing (as seen in older adults with age-related memory impairment). The BLA may be a key modulator of DG/CA3 and LEC in older adults with depressive symptoms, as we have found altered BLA activity in young (Leal et al., 2014a) and older adults (Leal et al., 2016b).

Materials and Methods

Participants

Forty-two participants (N = 42, 27 female; mean age 70.7 + 7.5SD were recruited from the local Orange County community via local campus announcements, flyers, and ads in local newspapers. Participants received monetary remuneration for their participation. Informed consent was obtained from all participants, with all procedures approved by the University of California, Irvine Institutional Review Board.

Inclusion/exclusion criteria

All participants underwent extensive neuropsychological evaluation during their visit. The battery was designed to examine memory function, as well as other aspects of general cognitive ability. The assessment included the following: (1) Mini-Mental State Examination (MMSE) to test global cognitive status, (2) Rey-Auditory Verbal Learning Test (RAVLT) to assess verbal learning, immediate, and delayed recall, (3) Digit Span backwards and forwards to assess working memory, (4) Trail Making Tests A and B to assess attention, visual search, and mental processing speed, (5) Beck Depression Inventory-II (BDI-II) and (6) Geriatric Depression Scale (GDS) to assess depressive symptoms, (7) Letter-Number Sequencing (LNS) and (8) Stroop Color and Word Test to assess executive function, (9) Beck Anxiety Inventory (BAI) to assess symptoms of anxiety, and (10) a modified version of the Pittsburgh Sleep Quality Index (PSQI) to assess sleep quality and recent stress (see Table 1 for results).

All participants were screened against major medical or psychiatric morbidities as well as substance abuse history, with the exception of a past or current diagnoses of depression and/or anxiety (N = 12 diagnosed with MDD, with 5 of those with comorbid anxiety in the DS+ group). Participants were selected for the DS+ group if they scored ≥4 on the GDS and ≥ 8 on the BDI-II. These scores indicate mild to severe levels of depression, where we ensured a range of symptom severity to examine the effects of LLD on a continuum. As expected, participants' GDS and BDI-II scores were positively correlated with one other

[Pearson's r = .907, p < .001; Fig S1], thus for all subsequent analyses we utilized the BDI-II, given its wider range of scores. Individuals taking anti-depressants were not excluded from the study (N = 10), however, these individuals were actively experiencing depressive symptoms and were considered non-responders. The goal of our study was to investigate how current depressive symptoms influenced MTL function, regardless of being on medication. Our final sample included 27 participants in the DS- group (18 female; mean age 72.2 + 7.6SD, mean BDI 3.0 + 3.6SD) and 15 participants in the DS+ group (9 female; mean age 67.9 + 6.9SD, mean BDI-II 22.2 + 9.1SD). Participants had no history of cognitive impairment or dementia. There were no significant differences between the groups in age, gender distribution, or cognitive status (MMSE) (p's > .05). All participants had normal or corrected-to-normal vision.

Imaging data collection

Functional MRI data were collected using a 3-Tesla Philips scanner with a 32-channel SENSE head coil. A single shot EPI sequence was used (1.5 mm isotropic voxels, 19 oblique axial slices parallel to the principal axis of the hippocampus, field of view = 180 × 28.3 mm × 180 mm, flip angle = 70°, SENSE factor = 2, TR/TE = 2200/26 ms, matrix size = 128 × 128). An additional high-resolution MPRAGE scan was also collected (0.65 mm isotropic resolution; 231 sagittal slices, field of view = 232 mm × 240 mm × 150 mm, flip angle = 18°, TR/TE = 11/5.03 ms, matrix size = 448 × 448).

Emotional discrimination task

Participants underwent an incidental encoding phase where they were shown emotional and non-emotional scenes, presented in randomized order, and were asked to rate the images for emotional valence (negative, neutral, and positive). Participants were given a subsequent surprise test 5 minutes after the encoding phase, in which they viewed another series of images, some of which were seen before in the incidental task (targets), some were similar, but not identical to ones seen in the incidental task (lures), and some were new (foils). Participants were asked to indicate whether items were "old" or "new" via button press. Participants were explicitly told that in order for an image to be called "old," it had to be the *exact* same image they saw before. The experiment consisted of 149 images during the study phase and 291 images during the test phase (Fig 1A). For more details on task development, see Leal et al., 2014b.

Image analysis

All data analyses were conducted using Analysis of Functional NeuroImages (AFNI) (Cox, 1996). Images were corrected for slice timing and subject motion. Motion censoring and scrubbing was accomplished using custom scripts (3 degrees or 2 mm). EPI images were co-registered to the MPRAGE scans using AFNI's align_epi_anat.py script. MPRAGE scans were aligned to high-resolution a custom anatomical template using Advanced Normalization Tools (ANTs) (Avants et al., 2011) which uses a powerful diffeomorphic algorithm (SyN) (Klein et al., 2009). The template included manual tracings of hippocampal subfields and has been used extensively by our lab in past studies (Leal et al., 2014a; Reagh and Yassa, 2014) and is defined according to the atlas of Duvernoy (Duvernoy, 2005). The subfields included the DG/CA3, CA1, subiculum (SUB) (Fig 1B) and were defined on

coronal slices along the anterior–posterior axis of the hippocampus. Representative slices in each hippocampus that best resembled the slices of Duvernoy were chosen and segmented according to the atlas description. The segmentation then proceeded from these slices in both directions slice by slice to ensure a smooth transition across slices.

Segmentations of entorhinal cortex into lateral (LEC) and medial (MEC) portions proceeded according to the procedures outlined in (Insausti et al., 1998). This procedure was carried out by using the lateral cortical fold forming the apex of the lower bank of the collateral sulcus as a guiding point for bisecting the entorhinal cortex. When performing this segmentation, we attempted to bisect the entorhinal cortex such that the medial and lateral ROIs were designated roughly equal portions of the overall volume. A divisional boundary was drawn roughly parallel to the apex of the white matter, perpendicular to the medial side of the surface of the entorhinal cortex. The LEC was of interest in the context of this experiment, thus, the MEC served as a control.

Amygdala segmentation procedures were based on (Entis et al., 2012). Three landmarks were identified on coronal slices along the anterior-posterior axis of the amygdala: 1) the medial tip of the alveus (up to the optic tract), 2) the most lateral point of the endorhinal sulcus, and 3) bottom of the circular sulcus. These three anatomical landmarks were easily observable and provided a reliable system for segmenting the amygdala subregions. After identifying the three anatomical landmarks, lines were drawn to connect the three points to each other, creating four quadrants which were then combined to form the BLA and CEA/CORT. The segmentation then proceeded from these slices in both directions slice by slice to ensure a smooth transition across slices. The CEA/CORT was used as a control region.

Behavioral vectors based on trial type (classified according to emotion and behavioral decision) were used to model the data using a deconvolution approach based on multiple linear regression. The resultant fit coefficients (betas) estimated activity versus an implicit baseline (novel foils) for a given time point and trial type in a voxel. This baseline has been used in many studies previously (Gabrieli, 1997; Stark and Squire, 2001; Kirwan et al., 2007; Leal et al., 2014a; Reagh et al., 2014b) and is useful in identifying brain regions associated with recollective success. As both lure trials and novel foils are visually similar, the difference in signals we see would be mostly due to differences in memory. Furthermore, while the choice of baseline in fMRI is arbitrary in many cases, it is better to choose an active baseline (such as novel foils) rather than a resting or fixation baseline (Stark and Squire, 2001). The sum of the fit coefficients over the expected hemodynamic response (3–12 s after trial onset) was taken as the model's estimate of the response to each trial type, relative to novel foils.

In order to investigate signals related to hippocampal pattern separation, we focused our analyses on lure trials that were either correctly rejected (accurate discrimination) or false alarmed (false recognition). These trials were contrasted against novel foils, where no memory-related signals were expected to occur. Activity on target trials was not considered in the main analyses, as these trials do not require hippocampal pattern separation.

Extracting ROI voxels

We selected voxels for subsequent analyses based on combining the voxels that changed with any of the task conditions. Active voxels were selected based on the overall F, agnostic to specific condition or contrast so as not to bias subsequent analyses and remove potential concerns regarding circularity and double-dipping (Kriegeskorte et al., 2009). This served to remove voxels that did not respond to any of the task conditions so that the analyses could be more sensitive to subtle changes across conditions. This voxel mask was then combined with anatomical ROI masks, resulting in hybrid functional/structural ROIs which were averaged and significance testing procedures were conducted on these averages.

Statistical analyses

All statistical analyses were conducted in SPSS v. 24 (IBM Corp., Armonk, NY). Planned comparisons were conducted using repeated-measures ANOVAs. Post hoc statistical tests were corrected for multiple comparisons using Scheffé's correction, with critical F values indicated in the text corresponding to the degrees of freedom (df) of the F-test (mentioned only once for each pair of df's), or Bonferroni correction where appropriate. Multiple comparisons corrections were not required for ROI analyses, as we had *a priori* hypotheses regarding specific MTL ROIs. All tests used the General Linear Model (ANOVA and correlations). Normality assumptions were investigated using Kolmogorov-Smirnov tests and all distributions investigated did not significantly deviate from the normal distribution. Repeated measures tests were corrected for error nonsphericity using Greenhouse-Geisser correction where appropriate. Mediation and moderation analyses were conducted in SPSS using the PROCESS module (Hayes, 2013). Unstandardized indirect effects were computed for each of 1,000 bootstrapped samples, and the 95% confidence interval was computed. Statistical values were considered significant at a final alpha level of .05 to prevent Type I error inflation.

Results

Depressive symptoms associated with enhanced negative discrimination

Participants performed the emotional discrimination task inside the scanner. During encoding, participants were instructed to rate the scenes for emotional valence as negative, neutral, or positive via button press. After a 5-minute delay, participants were given a surprise memory test, where they were shown the same scenes they saw before (targets), completely new images they had not seen before (foils), and similar but not identical scenes to what they saw before (lures) (Fig 1A, see Methods for more details). Participant demographic and neuropsychological test results are in Table 1.

We examined behavioral performance on the emotional discrimination task by calculating a lure discrimination index (LDI) for each emotion, calculated as p("New"|Lure) – p("New"|Target), and is a measure of how well participants discriminated among highly similar negative, neutral, and positive lures. We conducted a repeated-measures ANOVA with emotion (negative, neutral, and positive) as the within-subjects factor and group (DS+, DS-) as the between-subjects factor and found a significant effect of emotion [$F(2,78) = 3.57$, $p = .033$], where neutral information was remembered better than emotional information

[F(1,39) = 5.19, p = .028; Fig 2A]. We also found a significant effect of group [F(1,39) = 4.62, p = .038], where the DS+ group performed worse than the DS- group. We found a significant positive correlation between negative LDI and depressive symptoms (as measured by the Beck Depression Inventory-II, BDI-II) in the DS+ group [r = .618, p = .014] and not in the DS- group [r = −.024, p = .907; Fig 2B], which is consistent with our previous findings that depressive symptoms in young adults were associated with increased negative discrimination (Leal et al., 2014b).

Reduced DG/CA3 activity during negative discrimination and increased DG/CA3 activity during neutral discrimination in DS+ older adults

We utilized high-resolution (1.5 mm isotropic) fMRI to investigate MTL alterations in DS+ and DS- older adults during performance of the emotional discrimination task. We compared retrieval trials where similar lures were presented, since these trials were hypothesized to maximize interference, and analyzed both correct rejections (CRs, accurate discrimination) and false alarms (FAs, false recognition) of lures. It is important to note that neuroimaging analyses were conducted during specific behavioral conditions (CRs or FAs), which allows us to make inferences directly about the computational processes engaged during those conditions and prevents the analyses from being biased by participant performance. We focused on regions involved in emotional modulation of memory, which include the hippocampal subregions (DG/CA3, CA1, and SUB), the BLA, and the LEC (Fig 1B). We collapsed across left and right hemispheres as patterns looked similar across left and right. For control regions, we used the CEA/CORT and the MEC and found no significant differences in either region for all analyses (Fig S2).

To examine MTL differences during accurate discrimination in older adults with and without depressive symptoms, we conducted repeated-measures ANOVAs with emotion (negative, neutral, positive) and group (DS+, DS-) as factors for CRs in each ROI. We found an emotion × group interaction only in the DG/CA3 [F(2,80) = 3.42, p = .039; Fig 3A], where activity was reduced during negative discrimination and increased during neutral discrimination in the DS+ group [F(1,80) = 6.32, critical Scheffé = 6.22, p < .05]. We also tested whether there were any differences between anterior and posterior DG/CA3, but found no significant effects. To investigate if performance during negative and neutral discrimination tracked depressive symptom severity, we correlated BDI and the mean beta weight in DG/CA3 for negative and neutral trials. We found that the amount of DG/CA3 activity during neutral discrimination was positively correlated with depressive symptom severity [Pearson's r = .35, p = .022; Fig 3B]. This was not the case for negative trials, suggesting that the increased activity during neutral discrimination may be more related to depressive symptoms. This is consistent with previous literature suggesting that there are general episodic memory deficits in depression and that these may be related to hippocampal dysfunction (MacQueen and Frodl, 2011). Interestingly, recent studies in older adults have suggested that hippocampal hyperactivity may underlie memory deficits seen in aging (Yassa et al., 2011). Thus, the hyperactivity we see during neutral discrimination may be a marker for dysfunction.

DG/CA3 and BLA activity predict depressive symptoms during neutral discrimination

Given the known role of the BLA in emotional modulation (McGaugh, 2004), and our prior findings of amygdala alterations in depression (Leal et al., 2014a), we hypothesized that differences seen during DG/CA3 CRs could be linked to BLA activity, however, there were no significant group differences in BLA activity during accurate discrimination or correlations with DS severity for negative or neutral trials (all p's > .05; Fig S3). We hypothesized that the BLA's impact on DS severity may be mediated by the DG/CA3 during neutral discrimination, since DS severity seems to track hippocampal hyperactivity during neutral discrimination. In Step 1 of the mediation model, the regression of BLA activity during accurate neutral discrimination on DS severity, ignoring the mediator (DG/CA3 activity), was not significant [$\beta = 13.27$, $t(40) = 1.55$, $p = .128$]. Step 2 showed that the regression of BLA activity on DG/CA3 activity was significant [$\beta = .55$, $t(40) = 3.8$, $p < .001$]. Step 3 of the mediation process showed that DG/CA3 activity, controlling for BLA activity, on DS was not significant [$\beta = 16.38$, $t(39) = 1.79$, $p = .08$]. Step 4 of the analysis revealed that when controlling for DG/CA3 activity, BLA activity was not a significant predictor of the level of DS [$\beta = 4.33$, $t(39) = .45$, $p = .658$]. The bootstrapped unstandardized indirect effect was 8.94 and significantly differed from zero, as revealed by a 95% bootstrap confidence interval that was entirely above zero (confidence interval (CI): 1.77 to 23.52). Thus, greater BLA activity was associated with greater DG/CA3 activity during accurate neutral discrimination, which in turn was associated with higher levels of depressive symptoms (as both paths are positive; Fig 4, yellow panel). This suggests that greater activity in the amygdala-hippocampal network during discrimination is linked with greater depressive symptoms.

The impact of DG/CA3 and BLA activity on negative discrimination is moderated by depressive symptoms

Since we observed reduced activity during negative discrimination in the DS+ compared to DS- group, but found no correlation with depressive symptom severity, we decided to examine correlations within the DS+ and DS- groups to determine if there was any link between negative discrimination and DG/CA3 activity. We found a significant negative correlation between negative LDI and DG/CA3 activity during negative CRs in DS- [Pearson's $r = -.409$, $p = .034$] and a trend in the DS+ group in the opposite direction towards a positive correlation [Pearson's $r = .444$, $p = .098$]. We then compared r values using a Fisher's r to z transform and found a significant difference between correlations [DG/CA3: $z_{diff} = 2.58$, $p = .009$; Fig 5A]. Interestingly, these relationships appear to be in the opposite direction one would expect given the group averages (greater DG/CA3 activity in DS- compared to DS+), where the DS+ group shows greater DG/CA3 activity with better negative discrimination while the DS- group shows reduced DG/CA3 activity with better negative discrimination. The variability within the data suggests that DG/CA3 activity in each group tracks negative discrimination performance in opposing ways.

To determine if the level of symptom severity influenced the impact of DG/CA3 activity on negative discrimination, we conducted a moderation analysis using hierarchical linear regression (Hayes, 2013). The two predictors (DG/CA3 activity during negative discrimination and negative LDI) were entered into the regression analysis to determine each

predictor's effect on negative discrimination and then the interaction term was added. Results indicate that DG/CA3 activity [b = −.30, p = .026], but not BDI [b = .0004, p = .87] was associated with negative discrimination and overall did not account for a significant amount of variance in negative discrimination [R^2 = .149, F(3,38) = 2.22, p = .101]. However, the interaction between DG/CA3 activity and BDI explained a significant increase in variance in negative discrimination [ΔR^2 = .179, F(1,38) = 8.30, p = .007]. Thus, the influence of DG/CA3 activity on negative LDI was influenced by depressive symptom severity. The unstandardized simple slopes were tested for low (−1 SD below the mean), moderate (mean), and high (+1 SD above the mean) levels of the BDI and are shown in Figure 5B. Results suggest that the conditional effect of DG/CA3 activity on negative discrimination was present for high BDI scores (1 SD above the mean), but not for low or moderate BDI scores (p's > .05). To further characterize the nature of this interaction, we used the Johnson-Neyman technique, which identifies points in the range of the moderator variable where the effect of the predictor on the outcome transitions from being statistically significant to non-significant (Hayes, 2013). We found that when the BDI score was greater than or equal to 21.9, higher DG/CA3 activity led to higher negative LDI (Fig 5C). As can been seen, when the BDI ≥ 21.9, the confidence bands are entirely above zero (shaded grey).

While we did not find any group differences in the BLA, we wondered if a similar pattern was occurring in the BLA, as we would expect the prior effects to be driven by BLA activity. We performed the same analysis in the BLA and we found that DS- and DS+ groups showed opposing relationships between negative LDI and BLA activity during negative CRs [DS- Pearson's r = −.247, p = .214, DS+ Pearson's r = .402, p = .138] and found a marginally significant difference between the groups [BLA: z_{diff} = 1.92, p = .054; Fig 5D]. We performed a moderation analysis to determine if the effect of the BLA on negative discrimination depended on the level of depressive symptom severity (as in DG/CA3). The two predictors (BLA activity during negative discrimination and negative LDI) were entered into the regression analysis to determine each predictor's effect on negative discrimination and then the interaction term was added. Results indicate that BLA activity [b = −.30, p = .054] and BDI [b = −.0006, p = .82] was not associated with negative discrimination and overall did not account for a significant amount of variance in negative discrimination [R^2 = .116, F(3,38) = 1.66, p = .192]. However, the interaction between BLA activity and BDI explained a significant increase in variance in negative discrimination [ΔR^2 = .117, F(1,38) = 5.04, p = .031]. Thus, the influence of BLA activity on negative LDI was influenced by DS severity. The unstandardized simple slopes were tested for low (−1 SD below the mean), moderate (mean), and high (+1 SD above the mean) levels of the BDI and are shown in Figure 5E. Results suggest that the conditional effect of BLA activity on negative discrimination was present for high BDI scores (1 SD above the mean), but not for low or moderate BDI scores (p's > .05). To further characterize the nature of this interaction, we used the Johnson-Neyman technique and found that when the BDI score was greater than or equal to 27.2, higher BLA activity led to higher negative LDI (Fig 5F). We did not find any other correlations (across or within group) for any other trial types and conditions.

Increased hippocampal and LEC signals during positive false recognition in older adults with depressive symptoms

To examine MTL differences during false recognition in older adults with and without depressive symptoms, we conducted repeated-measures ANOVAs with emotion and group as factors for FAs in each ROI. During false recognition, we found significant group effects in the DG/CA3 [$F(1,40) = 8.12$, $p = .007$; Fig 6A], CA1 [$F(1,40) = 7.90$, $p = .008$; Fig 6B], and SUB [$F(1,40) = 6.02$, $p = .019$; Fig 6C], where the DS+ group showed increased activity compared to the DS- group across the entire hippocampus. We did not find any significant effects in the BLA (p's > .05). We wanted to determine if the group differences found during false recognition were linked to depressive symptom severity. The amount of activity only during positive false recognition was positively correlated with depressive symptoms in DG/CA3 [Pearson's $r = .30$, $p = .056$, marginal; Fig 6E], CA1 [Pearson's $r = .33$, $p = .032$; Fig 6F], and SUB [Pearson's $r = .37$, $p = .016$; Fig 6G]. Interestingly, in the LEC we found a significant effect of emotion [$F(2,80) = 3.96$, $p = .024$; Fig 6D] and a significant emotion × group interaction [$F(2,80) = 5.61$, $p = .006$]. There was increased activity only during positive false recognition in the DS+ group compared to the DS- group [$F(1,80) = 17.33$, $p < .001$]. Again, we found that the level of LEC activity during positive false recognition positively correlated with depressive symptom severity [Pearson's $r = .428$, $p = .006$; Fig 6H]. After correcting for multiple comparisons, we found that only the LEC correlation with DS during positive false recognition remained significant. Previous work in individuals with depression have shown deficits in positive memory processing (Dillon, 2015). It is interesting that we only see differences in positive lure processing during false recognition, when participants are incorrectly discriminating a positive lure item, suggesting these signals may be partially responsible for positive memory deficits observed in depressed individuals. While this remains speculative, it is possible that the LEC showed a unique activity profile for positive stimuli at least in part due to its connection with ventral tegmental area (VTA) dopamine neurons, which are associated with reward-related stimuli (Hutter and Chapman, 2013; Dillon, 2015).

LEC and BLA activity predict depressive symptoms during positive false recognition

Given the effects we found in the LEC during positive false recognition, we hypothesized that the BLA may influence depressive symptom severity, but might be mediated by LEC activity. In Step 1 of the mediation model, the regression of BLA activity during positive false recognition on level of DS, ignoring LEC activity, was not significant [$\beta = 9.46$, $t(40) = 1.47$, $p = .151$]. Step 2 showed that the regression of BLA activity on LEC activity was marginally significant [$\beta = .23$, $t(40) = 1.97$, $p = .056$]. Step 3 of the mediation process showed that LEC activity, controlling for BLA activity, was significant [$\beta = 21.55$, $t(39) = 2.63$, $p = .012$]. Step 4 of the analysis revealed that when controlling for LEC activity, BLA activity was not a significant predictor of the level of depressive symptoms [$\beta = 4.5$, $t(39) = .72$, $p = .478$]. The bootstrapped unstandardized indirect effect was 4.94 and significantly different from zero, as revealed by a 95% bootstrap confidence interval that was entirely above zero (CI: .439 to 15.66). Thus, greater BLA activity was associated with greater LEC activity during positive false recognition, which in turn was associated to greater depressive symptoms (as both paths are positive; Fig 4, blue panel).

Discussion

A summary of cognitive and neurobiological findings are shown in Table 2. We found that while DS+ older adults were generally impaired on the emotional mnemonic discrimination task relative to DS-, depressive symptom severity was positively associated with accurate discrimination of negative stimuli.

When examining activity during accurate discrimination, we observed reduced DG/CA3 activity during negative discrimination and increased DG/CA3 activity during neutral discrimination in DS+ older adults relative to DS- older adults. The increased DG/CA3 activity during neutral discrimination correlated with symptom severity, consistent with previous literature suggesting hippocampal hyperactivity may be dysfunctional (Wilson et al., 2006; Yassa et al., 2011; Bakker et al., 2012). During neutral discrimination, we found that the DG/CA3 mediates the relationship between BLA and depressive symptom severity such that greater BLA activity is associated with greater DG/CA3 activity, which is associated with greater depressive symptoms. This suggests that BLA—DG/CA3 activity is linked such that hyperactivity in these regions during neutral discrimination is associated with greater symptom severity. During negative discrimination, we examined correlations within DS+ and DS- groups and found that while DS+ older adults showed less DG/CA3 activity overall, the effect of DG/CA3 and BLA on negative lure discrimination depended on the level of depressive symptoms (greater depressive symptoms were associated with higher DG/CA3 and BLA activity). This suggests that increased activity in this network may be associated with higher levels of psychopathology, consistent with the idea that it is an aberrant (and perhaps reversible) condition.

During false recognition, we found that the entire hippocampus showed increased activity in older adults with depressive symptoms. However, the LEC showed increased activity in DS+ individuals selectively for positive information, the extent of which mediated the relationship between BLA activity and symptom severity. Consistent with the connectivity in this network (McDonald, 1984; Bell-McGinty et al., 2002), the impact of the BLA on the manifestation of depressive symptoms appears to be mediated by the LEC (during positive false recognition) and DG/CA3 (during neutral discrimination), implicating a particular amygdala-hippocampal pathway in depression. Selectivity of network dysfunction during positive false recognition in late-life depression may be due to the LEC's connection with ventral tegmental area dopamine neurons, which are associated with reward-related stimuli (Hutter and Chapman, 2013; Dillon, 2015). Furthermore, the "positivity effect" reported in aging (Mather and Carstensen, 2005) and a recent study from our lab showing the positivity effect is specific to older adults with age-related memory impairment (Leal et al., 2016a) suggests that older adults with depression may have hippocampal and entorhinal hyperactivity during positive false recognition that may underlie deficits in remembering positive information in depression (Dillon, 2015).

Based on our results, it appears that hyperactivity of the medial temporal lobe may underlie memory and mood dysfunction in late-life depression. In depressed older adults, hyperactivity in the DG/CA3 subregion and the BLA occurs during accurate memory performance of negative and neutral stimuli. Interestingly, hyperactivity also occurs during

false recognition, however this manifests only when remembering positive stimuli and may be more dependent on extrahippocampal cortices such as the lateral entorhinal cortex. Increases in activity, regardless of the type of stimuli, are all linked to greater depressive symptom severity. When linking activity to behavior on the mnemonic discrimination task, we find that greater DG/CA3 and BLA activity is associated with better discrimination of negative stimuli in depressed older adults, which may be an index of pathology. Increased activity levels appear to be linked to greater memory for negative stimuli, which may explain why depressed individuals exhibit negative ruminations.

Core vulnerability in the medial temporal lobes

Aging is associated with volume loss in the hippocampus (Golomb et al., 1996) which is thought to be partly due to synaptic loss rather than morphological cell loss (Rapp and Gallagher, 1996; Burke and Barnes, 2006). Several features have been consistently observed across species including perforant path degradation (Smith et al., 2000), CA3 hyperexcitability (Wilson et al., 2005; Yassa et al., 2011; El-Hayek et al., 2013; Haberman et al., 2013), and reduced DG neurogenesis (Kuhn et al., 1996; Gould, 1999) (for review, see Leal and Yassa, 2015). It is important to note that while many of these changes are reported in aging, it is impossible to know if these are pure aging effects or if they are confounded by preclinical dementia (Jagust, 2013). Hippocampal volume decreases in humans have also been noted in major depression (Sheline, 2011), and this also appears to be due to subtle synaptic changes in neuropil rather than frank cell loss (i.e. dendritic branching, spine complexity, etc.) in post-mortem human brain tissue (Stockmeier et al., 2004). Additionally, reduced DG neurogenesis (Dranovsky and Hen, 2006; Sahay and Hen, 2007; Miller and Hen, 2015), as well as retraction of the apical dendrites which make contact with the perforant path have been noted in the CA3 subfield of the hippocampus in chronically stressed rats (Conrad et al., 1999; Sousa et al., 2000). Thus, the same network appears to be vulnerable to the effects of both aging and depression.

In addition to structural and functional changes in the hippocampus, the amygdala also undergoes alterations in aging and depression. In aging, amygdala volume is relatively well-preserved (Kensinger, 2008), however, a reduction of noradrenergic input to the hippocampus (Kubanis and Zornetzer, 1981) as well as changes in peripheral epinephrine levels (Sternberg et al., 1985) have been reported in animal models of aging. Age-related alterations in synaptic plasticity in the amygdala-hippocampal network have also been reported (Almaguer et al., 2002). In depression, increases in amygdala volume have been reported, though this is not always the case (Drevets, 2001; Weniger et al., 2006; Drevets et al., 2008; Roozendaal et al., 2009; Dere et al., 2010). Functional imaging studies have demonstrated increased amygdala activity during negative memory encoding (Drevets, 2001; Sheline et al., 2001). Chronic stress models of depression in rodents have shown dendritic hypertrophy in the BLA (Vyas et al., 2002).

Determining how the MTL network is altered in the context of aging, depression, and the combination of the two is a crucial step that is necessary to develop therapeutic interventions to alleviate symptoms and potentially shift MTL structure and function back to a normal state or slow down progression. The number of depressive symptoms at baseline has been

shown to predict development of AD. With each additional symptom, risk of disease increased by about 20% (Wilson et al., 2002). Further investigation of the comorbidity between depression and aging, MCI, and AD is required to develop more targeted treatments for older adults with and without depressive symptoms with the goal of reducing the impact of depressive symptoms on progression of cognitive decline.

We suggest that the amygdala-hippocampal system described herein, which expresses alterations in LLD, is a system that is vulnerable to a wide range of brain pathologies and conditions, including other psychiatric disorders such as schizophrenia and bipolar disorder, as well as age-related cognitive decline and AD. It appears that one of the commonalities among all of these conditions is that they impose a type of chronic stress on the hippocampal formation and its extended networks that impacts memory function.

The majority of the DS+ older adults in our study were diagnosed with major depressive disorder (N = 12), but this was not an inclusion criterion for the current study. We opted to cut across traditional classifications of depression to understand psychopathology in a more integrative way by applying the NIMH Research Domain Criteria (RDoC) approach (Insel et al., 2010). Also consistent with the RDoC approach, a number of our participants were additionally suffering from comorbid anxiety symptoms (N = 5). Depression and anxiety are highly co-morbid with almost half of those with MDD also meeting criteria for anxiety disorders (Beekman et al., 2000), suggesting shared or common psychopathology.

Despite the focus of our hypotheses on the MTL, it is important to note that depression and age-related cognitive deficits are not limited to the MTL. We suspect there are frontal components that are also altered in the disease. Consistent with this, we find group differences in performance of tests that are sensitive to frontal dysfunction, including Trail Making Test B, and Stroop Test, as well as Letter-Number Sequencing. While the frontal lobes were beyond our field of view, future studies with whole brain fMRI could significantly inform on alterations exhibited by the frontal lobe, as well as connectivity between the MTL and the prefrontal cortex.

A particular limitation of the study is the absence of characterization of AD pathology. While all participants were cognitively intact, it is possible that some individuals were harboring AD pathology and thus may be more likely to exhibit cognitive decline in the future, however, this could not be tested in the current study. Another limitation of the study is that a number of DS+ participants were medicated (N = 10), however, they expressed symptoms regardless, thus our participants are a mixture of unmedicated and treatment-unresponsive individuals. Future studies could be more powered to examine the effects of anti-depressants in responders versus non-responders.

While aging, in and of itself, is associated with episodic memory impairment, further insults to the MTL system such as depression can further impair memory and alter hippocampal/amygdala dynamics. Overall, our results provide novel insight into hippocampal and amygdala subregional deficits that manifest in the context of LLD. Our emotional mnemonic discrimination task is a new candidate for a sensitive marker for LLD and may serve as a tool to assess outcomes in therapeutic trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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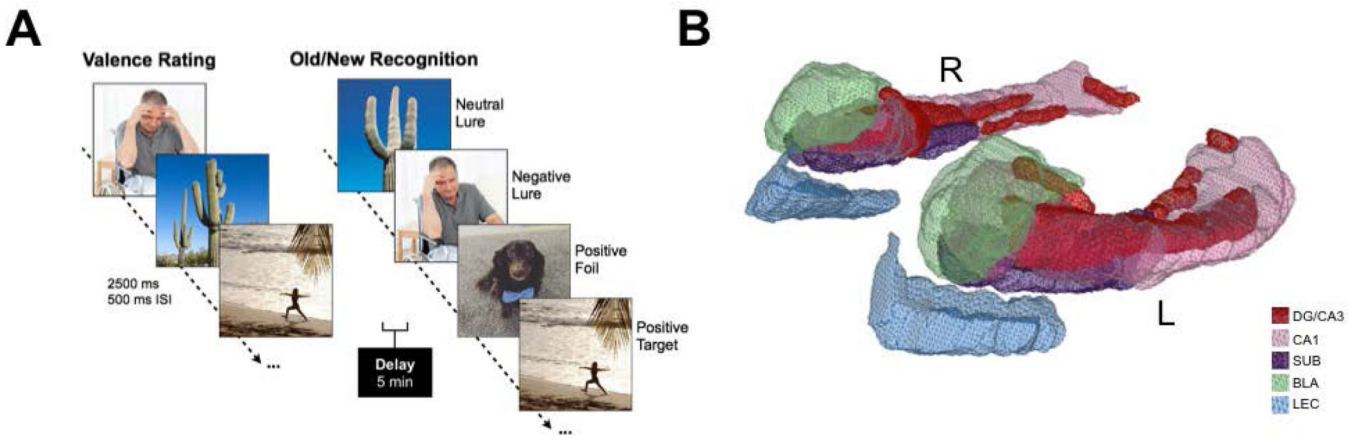

Figure 1. Emotional mnemonic discrimination task design and regions of interest

A) Participants performed the emotional mnemonic discrimination task. During encoding, participants rated images according to their emotional valence as negative, neutral, or positive. Each image was presented for 2500 ms with a 500 ms inter-stimulus-interval (ISI). After a 5-minute delay, participants underwent a surprise recognition test where they viewed negative, neutral, and positive targets, foils, and lures varying in similarity and were asked to indicate whether items were “old” or “new”, B) The schematic shows a 3D rendering of our high-resolution anatomical template including the dentate gyrus (DG)/CA3 (red), CA1 (pink), subiculum (SUB; purple), basolateral amygdala (BLA; green), and lateral entorhinal cortex (LEC, blue).

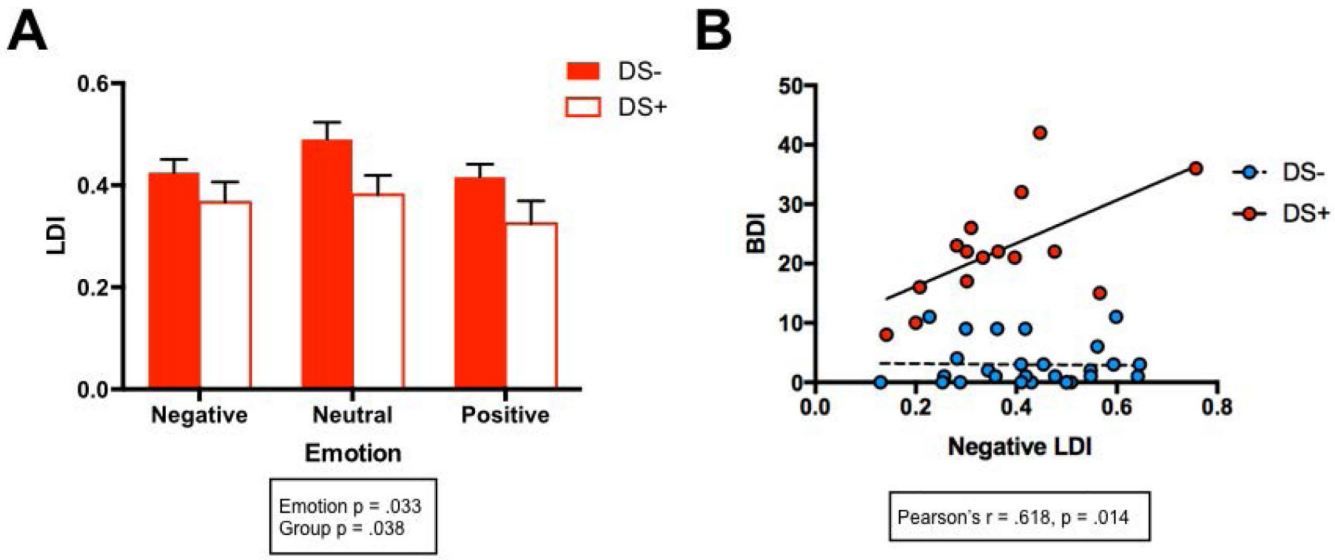

Figure 2. Behavioral performance on the emotional mnemonic discrimination task

A) Behavioral performance on the emotional mnemonic discrimination task in older adults with (DS+) and without (DS-) depressive symptoms, B) Positive correlation between negative lure discrimination index (LDI) and Beck Depression Inventory (BDI) score in DS+ older adults, with no such correlation in DS- older adults. Corresponding statistics are below each graph.

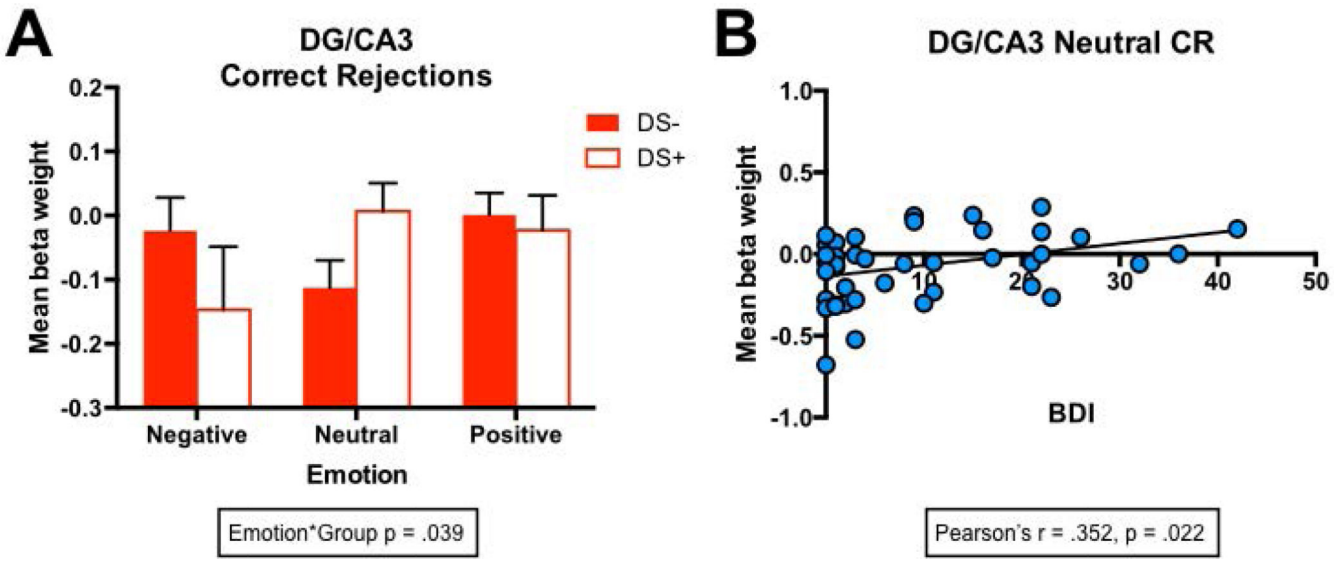

Figure 3. Activity in the DG/CA3 during emotional mnemonic discrimination task

A) Mean beta weight in DG/CA3 during correct rejections (CRs) across negative, neutral, and positive trials in older adults with (DS+) and without (DS-) depressive symptoms, B) Positive correlation between BDI and mean beta weight in DG/CA3 during neutral CRs.

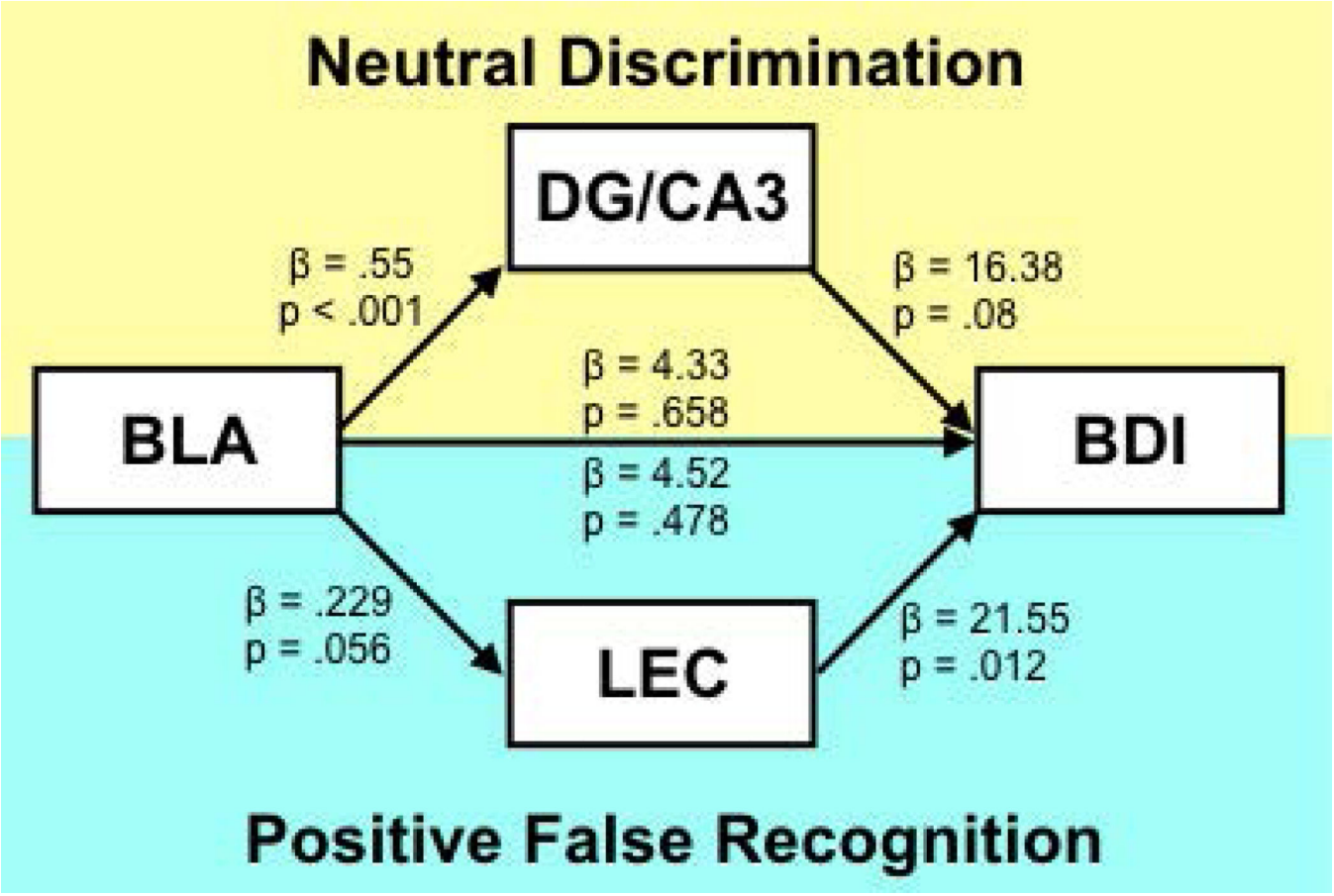

Figure 4. Mediation analyses examining the relationship between BLA and depressive symptom severity

Yellow (top) portion shows the mediation model that DG/CA3 mediates the relationship between BLA and depressive symptom severity during neutral discrimination. Blue (bottom) portion shows the mediation model that LEC mediates the relationship between BLA and depressive symptom severity during positive false recognition.

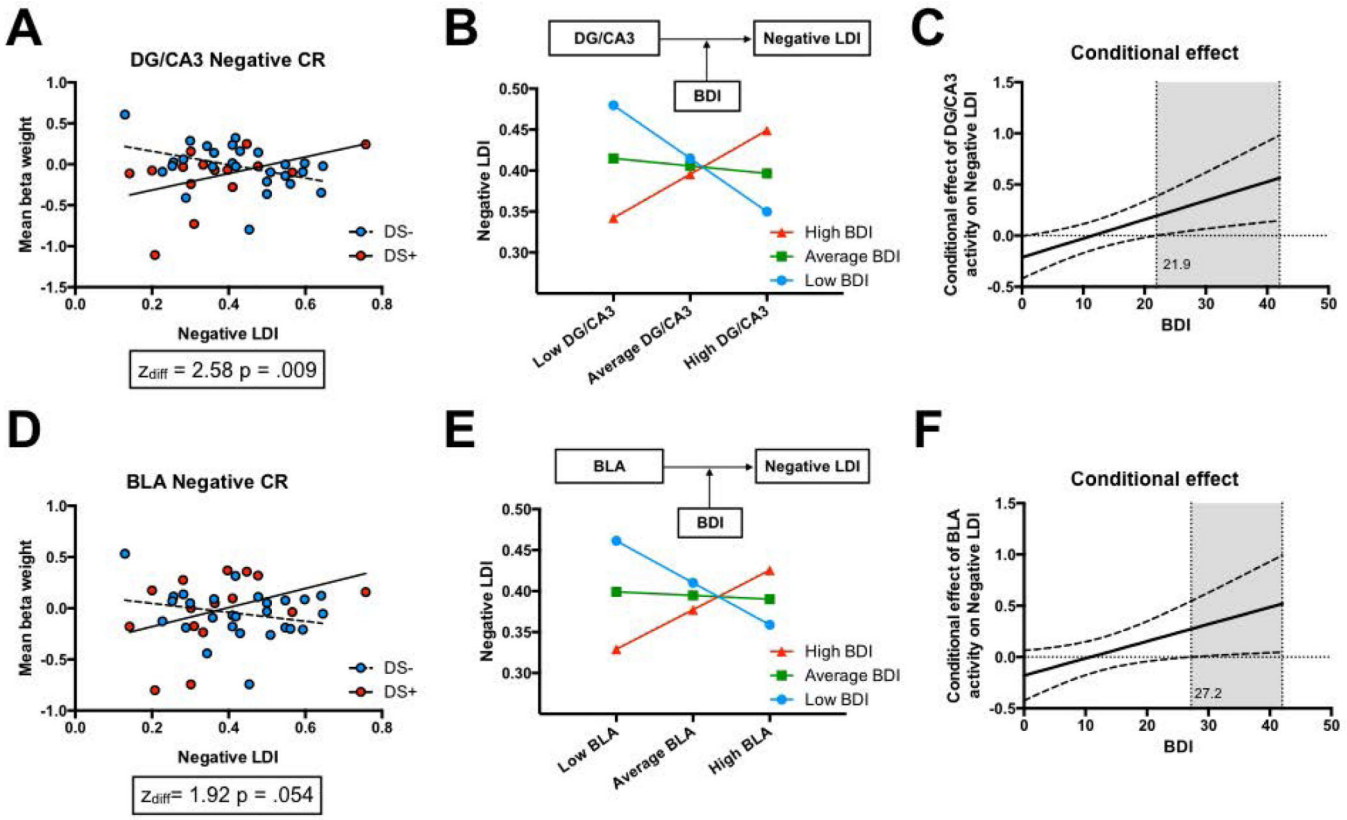

Figure 5. DG/CA3 and BLA activity during negative discrimination is associated with depressive symptom severity

A) Correlations between negative LDI and mean beta weight in DG/CA3 during negative CRs in DS+ and DS- groups, B) Visualization of moderation analysis showing the influence of the DG/CA3 on negative LDI is moderated by depressive symptom severity, C) Visualization of the specificity of the conditional effect of DG/CA3 on negative LDI, D) Correlations between negative LDI and mean beta weight in BLA during negative CRs in DS+ and DS- groups, E) Visualization of moderation analysis showing the influence of the BLA on negative LDI is moderated by depressive symptom severity, F) Visualization of the specificity of the conditional effect of BLA on negative LDI.

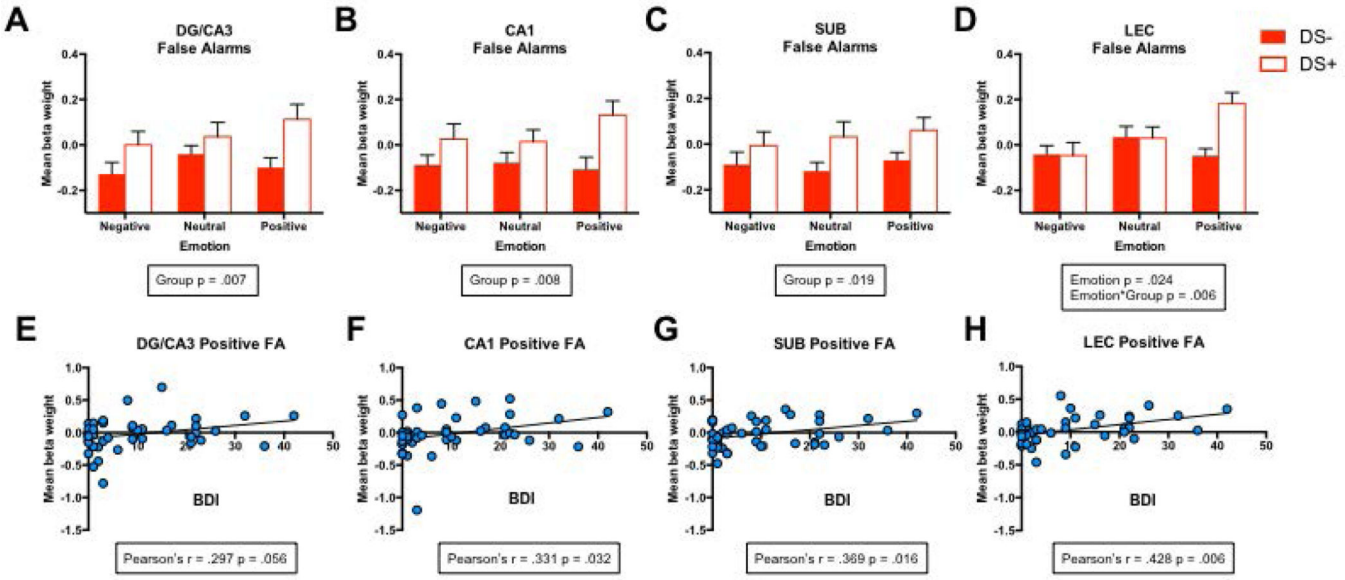

Figure 6. Activity in hippocampal subfields and LEC during false recognition

A) Mean beta weight in DG/CA3 during false alarms (FAs) across negative, neutral, and positive trials in DS+ and DS- groups, B) Mean beta weight in CA1 during FAs across negative, neutral, and positive trials in DS+ and DS- groups, C) Mean beta weight in SUB during FAs across negative, neutral, and positive trials in DS+ and DS- groups, D) Mean beta weight in LEC FAs across negative, neutral, and positive trials in DS+ and DS- older adults, E) Positive correlation between BDI and DG/CA3 activity during positive FAs, F) Positive correlation between BDI and CA1 activity during positive FAs,G) Positive correlation between BDI and SUB activity during positive FAs, H) Positive correlation between BDI and LEC activity during positive FAs. Error bars are ± S.E.M. Corresponding statistics are below each graph.

Table 1

Participant demographics and neuropsychological test results.

Groups	DS−	DS+
Sample size	27	15
M:F	9:18	6:9
Age (SD)	72.2 (7.6)	67.9 (6.9)
*Education (SD)	16.7 (2.2)	13.9 (2.2)
Variables	**Mean, SEM**	**Mean, SEM**
Digit Span Forward	10.1, 0.3	9.9, 0.5
Digit Span Backward	6.4, 0.4	6.1, 0.5
*Letter-Number Sequencing	19.0, 0.4	16.5, 1.0
*Geriatric Depression Scale	0.8, 0.2	7.4, 0.7
Mini Mental State Exam	28.9, 0.2	28.1, 0.5
*RAVLT Immediate Recall	11.0, 0.6	7.7, 1.0
*RAVLT Delayed Recall	10.6, 0.7	7.5, 1.0
RAVLT Recognition Recall	13.9, 0.3	13.4, 0.6
Trail Making Test A	29.7, 1.2	36.0, 4.3
*Trail Making Test B	73.8, 5.7	107.1, 11.5
*Stroop (Word-Color)	32.8, 1.7	26.5, 1.6
*Beck Anxiety Inventory	3.9, 0.7	13.9, 2.7
*Beck Depression Inventory-II	3.0, 0.7	22.2, 2.4
Hours of Sleep (night before)	7.9, 0.2	8.3, 0.5
*Level of stress (past month, 1–7)	2.3, 0.2	4.4, 0.4

* Significantly different between groups; Education [$t(40) = -3.8$, $p < .001$], Letter-Number Sequencing [$t(40) = -2.5$, $p = .02$], Geriatric Depression Scale [$t(40) = 10.5$, $p < .001$], RAVLT immediate recall [$t(40) = -2.9$, $p = .01$], RAVLT delayed recall [$t(40) = -2.6$, $p = .01$], Trail Making Test B [$t(40) = 1.9$, $p = .01$], Stroop Test (Word-Color) [$t(40) = -2.4$, $p = .02$], Beck Anxiety Inventory [$t(40) = 4.6$, $p < .001$], Beck Depression Inventory [$t(40) = 9.7$, $p < .001$], Level of stress [$t(40) = 4.5$, $p < .001$].

Table 2

Summary of cognitive and neurobiological findings in DS+ compared to DS- older adults.

Cognitive Findings		**Neurobiological Findings**	
Negative		Negative	
1	Impaired discrimination in DS+ group.	**1**	Reduced DG/CA3 activity in DS+ (dis)
2	Positive correlation between BDI and negative discrimination in DS+ group.	**2**	Influence of DG/CA3 and BLA on discrimination depends on DS
Neutral		Neutral	
1	Impaired discrimination in DS+ group.	**1**	Increased DG/CA3 in DS+ (dis)
		2	DG/CA3 mediates BLA's effect on DS during discrimination
Positive		Positive	
1	Impaired discrimination in DS+ group.	**1**	Increased LEC activity in DS+ (false rec)
		2	LEC mediates BLA's effect on DS during false recognition