Negative Emotional Verbal Memory Biases in Mild Cognitive Impairment and Late-Onset Depression

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Objective: *Early and preferential targeting of limbic structures by Alzheimer disease (AD)-related pathology suggests emotion dysregulation may serve as a marker of AD risk.We studied emotional verbal memory in two groups at risk for AD, amnestic mild cognitive impairment (aMCI) and late-onset depression (LOD), to test the hypothesis that aMCI and LOD would be characterized by a negative bias in emotional memory, whereas cognitively normal (CN) adults would show the "positivity effect" associated with healthy aging.* **Methods:** *Participants completed a novel test of emotional verbal memory, the Emotional Verbal Learning Test (EVeLT), consisting of a 15-item list of words with positive, negative, or neutral valence. Recall as a function of group and valence was analyzed using mixed analysis of variance. Spearman's rho was used to examine associations between EVeLT, mood, and executive function. MCI and CN participants had no current or past history of mood or anxiety disorders. aMCI participants met neuropsychological criteria for single-domain aMCI (sd-aMCI). LOD developed their first episode of depression at ≥60 years of age.* **Results:** *CN adults recalled more positive words, whereas sd-aMCI and LOD adults recalled more negative, relative to neutral, words on the EVeLT. Positive emotional memory and negative attitudes regarding self were inversely correlated in CN adults.* **Conclusion:** *sd-aMCI and LOD groups show negative emotional memory biases, consistent with our hypothesis that emotion dysregulation is a signature of AD risk.* (Am J Geriatr Psychiatry 2017; 25:1160–1170)

Key Words: Mild cognitive impairment, geriatric depression, emotion, memory

INTRODUCTION

Neuropathologic and neuroimaging studies indicate that before onset of memory deficits, the main pathologic substrates of Alzheimer disease (AD) have accumulated in limbic regions that support regulation of emotion and memory processes related to emotion.[1–4] This limbic network is composed of the entorhinal cortex and hippocampus; the neocortex

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surrounding the corpus callosum, namely the insula, orbitofrontal, ventral anterior cingulate, cingulate, and parahippocampal cortices; and subcortical structures including the amygdala, hypothalamus, and thalamus.[5] Neurofibrillary tangles distribute in a hierarchical pattern, appearing first in the transentorhinal cortex, followed by entorhinal cortex, hippocampus, and amygdala,[6] before propagating to the association cortices, where they concentrate most densely in the ventral anterior cingulate cortex, orbitofrontal cortex, and insula.[7] Amyloid plaques similarly appear to accumulate first in a limbic network comprised of amygdala, ventral anterior cingulate cortex, and hippocampus formation, which appear to exhibit "hub" properties in the β-amyloid network, suggesting amyloid plaques may disperse throughout the brain along limbic pathways.[8]

Through reciprocal connectivity with entorhinal cortex and hippocampus, the amygdala mediates emotional enhancement of memory (EEM), such that recall is better for emotionally salient compared with neutral information.[2] EEM has been well studied in cognitively normal (CN) older adults and in depression. Older CN adults show a "positivity bias" in memory for positively valenced information (Pos-EEM) relative to young adults, who are biased toward greater recall of negative, relative to neutral material.[9] Greater prefrontal cortex activity and cognitive control over affective responses to negatively valenced information is hypothesized to mediate the positivity bias in healthy aging.[9] In contrast, depression is characterized by emotion dysregulation and greater attention and memory for negative information[4] as a consequence of abnormally elevated amygdalar activity and decreased amygdalar–prefrontal cortex coupling.[4] Although negative biases have been demonstrated specifically in older adults with depression,[10–15] the evidence is inconsistent.[13,16,17] This may result from failing to account for age at onset,[13] because depression beginning at age 60 years or older (late-onset depression [LOD]) may be a prodrome of AD based on epidemiologic studies.[18] Notably, a functional magnetic resonance imaging study of LOD failed to detect evidence of negatively biased behavioral responses or heightened limbic activity to negative words.[16]

The early involvement of AD pathology in limbic regions suggests that alterations in EEM may manifest before onset of clinically significant memory impairment. This is supported by animal models of healthy aging and AD indicating that changes in EEM precede deterioration in spatial memory and other cognitive abilities.[19,20] Whether EEM is altered in the AD prodrome of mild cognitive impairment (MCI) is unclear. Although absence of EEM has been reported in individuals with amnestic MCI (aMCI) compared with those who are CN,[21] most studies show no differences in EEM between MCI and CN individuals.[15,22–29] However, post-hoc analyses suggest subtle changes in EEM in MCI. Although MCI did not differ from CN individuals in overall performance on an emotional variant of the Deese–Roediger–McDermott paradigm, they recalled more depression-relevant words than neutral compared with CN adults.[24] Similarly, group × valence effects were not detected in wordlist learning, but MCI adults learned negative words at a faster *rate* than neutral over trials compared with those who were CN.[22] MCI groups also performed better on an emotional working memory task when target pictures were negative as opposed to neutral or positive.[30] These findings suggest that the earliest stages of AD may be characterized by negative biases in EEM (Neg-EEM).

The EEM effect is variable across studies, with reports of absence of EEM,[22–26] EEM for both positive and negative information,[25,29] or EEM for either positively or negatively valenced material in CN and MCI samples.[4,15,21,27,28] This variability implies that EEM is susceptible to task, stimulus, or sample characteristics.[31] One consistent finding is that EEM is more likely to be detected when emotional and neutral stimuli are mixed in a single, as opposed to separate, list.[32] Thus, studies of wordlist learning that use lists blocked by valence[24] are less likely to detect EEM.

Changes in emotional memory may also vary according to the extent of AD pathology within limbic networks. Studies that include various stages of MCI may fail to identify robust group differences between MCI and CN persons due to heterogeneity within the MCI sample. Whether this factor has contributed to the discrepancy in findings across studies is unclear because previous studies of emotional memory in MCI do not uniformly report neuropsychological profiles of MCI participants[22,26] (but see Brueckner and Moritz).[24]

In the current study we sought to address limitations of the extant literature by comparing performance of single-domain amnestic MCI (sd-aMCI), LOD, and CN older adults on a task that we developed to evaluate EEM based on emotional wordlist learning. We chose to study sd-aMCI, characterized by memory

impairment while other cognitive domains are intact, because sd-aMCI may represent an earlier and homogeneous AD prodrome than aMCI with multiple cognitive deficits.[33,34] Our overall hypothesis is that sd-aMCI and LOD are characterized by deficits in emotion regulation as a consequence of abnormalities in structure or function of limbic regions. Therefore, we predicted a dissociation such that sd-aMCI and LOD would show Neg-EEM relative to CN adults, whereas CN adults would show Pos-EEM.

To explore potential mechanisms for EEM, we assessed the associations between Pos-/Neg-EEM and measures of mood and executive function within groups. Based on the literature on mood-congruent cognitive biases, we expected that mood and anxiety would directly correlate with Neg-EEM and inversely associate with Pos-EEM. Based on the cognitive control theory for the positivity bias associated with healthy aging,[9] we expected executive function would correlate with Pos-EEM and inversely correlate with NEG-EEM.

METHODS

Participants

Sixteen sd-aMCI adults (3 men; mean age: 73.5 [standard deviation {SD}: 7.0]), 16 LOD adults (5 men; mean age: 72 [SD: 8.7]), and 16 CN adults (4 men; mean age: 69 [SD: 4.14]) participated. Recruitment sources were mood and memory clinics, research volunteer database, and community advertising.

General eligibility criteria were English language proficiency; Mini-Mental Status Exam[35] ≥ 26; and no history of neurologic disorders, unstable medical conditions, or current psychotropic medications because of potential impact on neuropsychological performance and emotional processing.[36]

sd-aMCI memory impairment was defined as performance on at least two neuropsychological tests of memory at least 1.5 SDs lower than expected relative to overall intellect, with other cognitive domains intact,[37] preservation of independence in functional abilities, and exclusion of psychiatric and medical causes of cognitive decline.

For the LOD sample, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for major depressive disorder diagnoses were established by a board-certified psychiatrist. Eligibility criteria included onset of initial major depressive episode ≥ 60 years of age and Hamilton Depression Rating Scale scores ≥ 15. Table 1 provides additional clinical characteristics. For the CN group inclusion criteria were no subjective or objective memory deficits based on neuropsychological assessment and no current/ lifetime history of psychiatric illness.

Participants received monetary compensation. The study was approved by Baycrest's Research Ethics Board.

Assessments

Emotional Verbal Learning Test

We developed the Emotional Verbal Learning Test (EVeLT) by selecting words from a database of personality adjectives rated for likeability,[38] which closely corresponds to valence, to create a 15-word list with 5 each of positive, negative, and neutral personality adjectives that were randomly sequenced. Positive, neutral, and negative words were selected from the top, middle, and bottom tertile of the list, respectively. Words differed in likeability and valence as intended: likeability: positive, mean: 437.6; SD: 21.3; neutral, mean: 346.8; SD: 40.0; negative, mean: 159.8; SD: 28.2; $F(2,12)$ 106.4, $p < 0.001$; all pair-wise comparisons [Tukey HSD-corrected] significant, $p \leq 0.001$; valence: positive, mean: 5.76; SD: 0.34; neutral, mean: 4.0; SD: 0.85; negative, mean: 2.13; SD: 0.32; $F(2,12) = 53.0$, $p < 0.001$; all pair-wise comparisons significant, $p \leq 0.001$). A multivariate analysis of variance (ANOVA) of arousal, frequency, familiarity, and length of words showed no significant effect of valence ($F(8,20) = 2.3$, $p = 0.063$).

All participants were administered the same word list, which was read aloud by a trained research assistant. Participants were instructed to listen to the entire word list and try to remember as many words as possible in any order (free recall). After the participant's responses, the word list was read aloud again by the research assistant, followed by free recall, for a total of five trials with no breaks between trials.

Cognitive Measures

Participants were administered the Mattis Dementia Rating Scale and a neuropsychological battery

TABLE 1. Demographic And Clinical Characteristics of sd-aMCI, LOD, and CN Groups

Variable	CN Group (N = 16)	sd-aMCI Group (N = 16)	LOD Group (N = 16)
Age at baseline, yr	69.3 (4.1)	73.5 (7.0)	71.9 (8.7)
No. of women in sample	12	13	11
Ethnicity			
White	16	16	14
Asian	0	0	2
Education, yr	16.8 (2.5)	15.6 (3.5)	15.8 (3.5)
Cumulative Illness Rating Scale for Geriatrics	3.8 (2.5)	6.1 (4.3)	7.9 (3.7) [a]
Mini-Mental Status Exam	29.3 (1.6)	27.8 (1.6) [c]	28.9 (1.5)
Mattis Dementia Rating Scale	137.2 (8.3)	136.1 (7.9)	137.9 (5.1)
Geriatric Depression Scale	0.9 (1.1)	2.1 (2.8)	7.9 (4.1) [a,b]
Spielberger State-Trait Anxiety Scale			
State anxiety	28.1 (8.6)	32.0 (8.6)	44.9 (9.8) [a,b]
Trait anxiety	29.9 (7.1)	31.6 (10.1)	52.1 (11.2) [a,b]
Dysfunctional Attitudes Scale	101.7 (23.9)	91.0 (19.9)	130 (22.9) [a,b]
Recurrent major depressive disorder (N)			4
Any previous treatment for major depressive disorder (N)			
Antidepressant medication			1
Psychotherapy			1
Both antidepressant and psychotherapy			2
Days between psychiatric assessment and study testing			6.5 (5.8)
Treatment at time of study entry (N)			
Psychotropic medications			0
Non-pharmacological treatments			2

Notes: Summary statistics are mean (SD) for continuous measures. All statistically significant results as assessed using ANOVA [F(2, 36)] > 1, followed by pair-wise comparisons using Tukey test.
[a]LOD > CN, $p < 0.05$.
[b]LOD > sd-aMCI, $p < 0.05$.
[c]sd-aMCI < CN, $p < 0.05$.

(Table 2). Neuropsychological testing was conducted to confirm sd-aMCI participants were impaired in memory but not in any other cognitive domain and to confirm that CN and LOD participants did not meet neuropsychological criteria for MCI. Because of participant fatigue and an administrative error, the entire neuropsychological battery was not conducted in all participants, particularly in the LOD group, who were unmedicated. In all cases, however, neuropsychological testing provided an accurate assessment of cognitive status and confirmed diagnostic grouping.

Mood Measures

Participants completed the following self-report measures of mood in a separate testing session from cognitive assessments: the Geriatric Depression Scale (GDS), a standard clinical measure of depression in older adults;[39] the State-Trait Anxiety Inventory;[40] and the Dysfunctional Attitudes Scale (DAS).[41] The DAS is a measure of negative attitudes reflecting dysfunctional contingencies for self-worth (e.g., "I am not likeable if I fail the task") that are relatively enduring, rather than a mood-state dependent, and may be a trait marker of cognitive vulnerability toward depression because it is predictive of relapse.[42]

Statistical Analyses

The number of correctly recalled words over the five trials was totaled by valence (POS-recall, NEG-recall, NEU-recall) and analyzed using a mixed ANOVA to assess group differences in EEM. Pos-EEM and Neg-EEM were computed as the difference between number of emotionally valenced and neutral words recalled (Pos-EEM = POS-recall-NEU-recall; Neg-EEM = NEG-recall-NEU-recall) for each participant. Statistical

TABLE 2. Neuropsychological Performance of sd-aMCI, LOD, and CN Groups

	CN Group[a]		sd-aMCI Group		LOD[a]	
Test Name	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**
Wechsler Abbreviated Scale of Intelligence						
Block Design	14	35.64 (13.30)	16	37.06 (15.16)	8	41.25 (12.78)
Matrix Reasoning	14	26.00 (2.57)	16	22.63 (6.65)	10	20.40 (8.66)
Wechsler Adult Intelligence Scale–III						
Vocabulary	15	56.87 (6.01)	15	53.73 (5.01)	13	49.23 (10.20) [b]
Boston Naming Test	14	56.86 (2.21)	16	55.19 (2.61)	6	47.50 (15.18) [b]
Delis-Kaplan Executive Function System						
Phonemic Fluency	16	48.00 (8.88)	16	44.25 (13.62)	13	43.69 (15.39)
Category Fluency	16	22.19 (5.50)	16	17.63 (2.73)	9	24.00 (19.97)
Card Sorting Test	10	10.18 (2.09)	15	10.73 (6.99)	13	9.08 (3.62)
Trail Making Test Number Letter Sequencing, sec	16	83.81 (30.91)	15	94.00 (28.55)	14	102.86 (36.07)
Color Word Interference Task Inhibition, sec	14	58.57 (10.65)	16	59.81 (10.68)	14	55.64 (11.02)
Wechsler Memory Scale-Revised						
Logical Memory Immediate Recall	16	28.19 (7.09)	16	19.93 (6.22) [c d]	13	27.31 (7.55)
Logical Memory Delayed Recall	16	28.25 (8.74)	16	17.69 (8.02) [c]	13	28.00 (7.53)
California Verbal Learning Test-II						
List A Learning (Trials 1–5)	16	53.19 (10.09)	16	36.25 (9.26) [f g]	15	50.07 (13.35)
List A Long Delay Free Recall	16	11.56 (2.80)	16	5.25 (3.84) [e,f]	15	10.60 (3.46)
List A Long Delay Cued Recall	16	12.5 (2.56)	16	6.75 (3.62) [e,f]	15	11.07 (3.04)
Brief Visuospatial Memory Test-Revised						
Immediate Recall	16	23.31 (5.19)	16	16.19 (6.99) [c]	13	19.54 (4.10)
Delayed Recall	16	9.50 (1.75)	16	6.13 (3.20) [d,f]	13	8.46 (2.03)

Notes: [a] Missing data, see text page ••.
Significantly different from CN group as assessed using one-way ANOVA followed by Tukey post hoc tests: [b]p ≤0.05, [c]p ≤0.01, [f]p ≤0.001.
Significantly different from LOD group as assessed using one-way ANOVA followed by Tukey posthoc tests: [d]p ≤0.05, [g]p ≤0.01, [e]p ≤0.001.

significance of Pos-/Neg-EEM was evaluated using one-sample t tests.

To explore potential mechanisms for EEM, correlations between Pos-/Neg-EEM and measures of mood and executive function were performed using Spearman's rho (r_s) due to non-normality of mood and executive measures.[a] Pos- and Neg-EEM were correlated with GDS, State-Trait Anxiety Inventory, and DAS within each group. Hochberg's step-up version of the Bonferroni test[43] was used to correct for six comparisons within groups.

Pos- and Neg-EEM scores were correlated with executive measures within each group: F-A-S letter fluency, Card Sorting Task, Trail Making Test-B, and Stroop Color-Word Test from the Delis-Kaplan Executive Function System battery. Hochberg's step-up version of the Bonferroni test[43] was used to correct for eight comparisons within groups.

RESULTS

Demographic and Clinical Characteristics of Groups

Groups did not differ in age or education (Table 1). The sd-aMCI group scored lower on the Mini-Mental Status Exam compared with the CN group, whereas LOD and CN groups did not differ. The LOD group scored significantly higher on mood and anxiety measures relative to both sd-aMCI and CN groups, whereas sd-aMCI and CN groups did not differ. The mean GDS score of 7.9 (SD: 4.1) in the LOD group is in line with validation studies of the GDS in community samples of older adults that report means ranging from 7.3 to 9.8[44–46] and that indicate cut-off scores of four or below[47–50] yield adequate sensitivity and specificity.

[a]Group comparisons using the Kruskal-Wallis test for these and other non-normally distributed measures in Tables 1 and 2 yielded similar results as ANOVA. For consistency, we have reported the results of ANOVA in Tables 1 and 2 for both normally and non-normally distributed measures.

TABLE 3. Performance on EVeLT in sd-aMCI, OD, and CN Groups

Correctly Recalled Words	CN Group (N = 16) Mean (SD)	Sd-aMCI Group (N = 16) Mean (SD)	LOD Group (N = 16) Mean (SD)	Total (N = 48) Mean (SD)
Positive	15.06 (4.14)	7.63 (3.01)	9.13 (4.16)	10.85 (5.17)
Negative	14.06 (3.11)	13.25 (2.72)	12.69 (4.08)	13.33 (3.33)
Neutral	12.00 (3.74)	7.56 (3.71)	9.13 (4.16)	9.56 (4.22)
Total	41.13 (8.18)	28.44 (6.26)	31.69 (11.52)	33.75 (10.29)

Neuropsychological Performance

Table 2 shows the neuropsychological performance for all groups. The sd-aMCI group scored lower on all memory tests compared with CN and LOD groups. The LOD group differed from the CN group on Wechsler Adult Intelligence Scale vocabulary and the Boston Naming Test (likely because of fewer native English speakers). Executive function did not differ among groups.

EVeLT Performance

Mean POS-, NEG-, and NEU-recall scores by group are summarized in Table 3. ANOVA revealed main effects of group and valence ($F(2,45)$ 8.71, $p = 0.001$; $F(2,90) = 19.8$, $p < 0.001$, respectively) and a group × valence interaction ($F(4,90) = 4.6$, $p = 0.002$). Post-hoc tests using the Sidak adjustment for multiple comparisons at $p < 0.05$ showed that sd-aMCI and LOD groups scored lower overall on the EVeLT compared with CN adults (CN > sd-aMCI: Difference = 4.35, 95% confidence interval [CI]: 1.73–6.98; CN > LOD: Difference = 2.85, 95% CI: 0.225–5.48). The main effect of valence was explained by greater POS- and NEG-recall relative to NEU-recall (POS > NEU: Difference = 1.44, 95% CI: 0.07–2.81; NEG > NEU: Difference = 3.79, 95% CI: 2.17–5.41), and significantly higher NEG-recall compared with POS-recall (Difference = 2.35, 95% CI: 0.83–3.88).

The group × valence interaction was explained by greater POS-recall compared with NEU-recall in CN adults only (CN: Difference = 3.06, 95% CI: 0.69–5.44; sd-aMCI: Difference = 0.44, 95% CI: –1.94 to 2.81; LOD: Difference = 0.81, 95% CI: –1.56 to 3.19) and greater NEG-recall compared with POS- or NEU-recall in sd-aMCI and LOD groups (NEG > POS: sd-aMCI: Difference = 5.19, 95% CI: 2.55–7.83; LOD: Difference = 2.94, 95% CI: 0.30–5.58; NEG > NEU: sd-aMCI: Difference = 5.63, 95% CI: 2.82–8.43; LOD: Difference = 3.75, 95% CI: 0.94–6.56), with no differences found in CN participants (NEG > POS: Difference = –1.06, 95% CI: –3.70 to 1.58; NEG > NEU: Difference = 2.00, 95% CI: –0.81 to 4.81). These patterns were unchanged when two non-white LOD participants were removed from analysis.

Emotional Memory Biases

Figure 1 shows group differences in emotional enhancement of memory. Pos-EEM was significant in CN participants only (Pos-EEM: mean: 3.06, SD: 3.75, $t(15) = 3.27$, $p = 0.005$; Neg-EEM: mean: 2.00, SD: 4.47, $t(15) = 1.79$, $p = 0.094$), and Neg-EEM was significant in aMCI and LOD groups only (aMCI: Neg-EEM: mean: 5.63; SD: 5.33, $t(15) = 4.22$, $p = 0.001$; Pos-EEM: mean: 0.44, SD: 3.29, $t(15) = 0.53$, $p = 0.60$; LOD: Neg-EEM: mean: 3.75, SD: 3.62, $t(15) = 4.14$, $p = 0.001$; Pos-EEM: mean: 0.82, SD: 4.37, $t(15) = 0.74$, $p = 0.47$).

Association between EEM and Mood

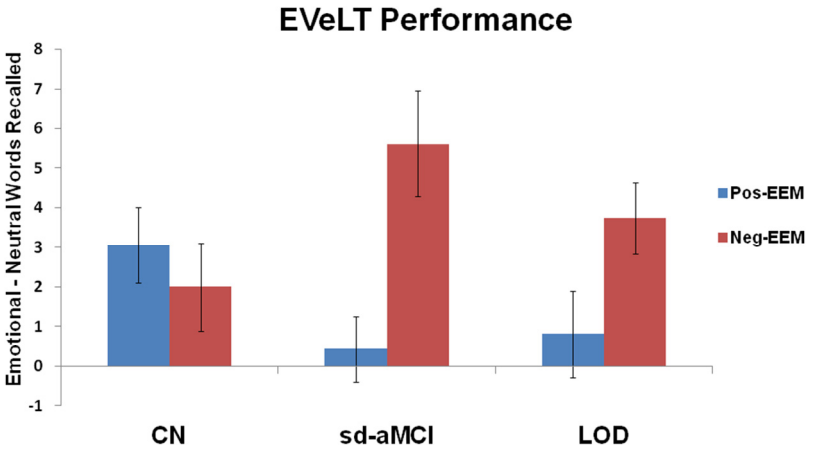
Pos-EEM and DAS were inversely correlated in CN adults ($r_s = –0.64$, $p = 0.008$) and remained statistically significant after multiple comparisons correction (Table 4).

TABLE 4. Correlations Between Emotional Bias Memory Scores and Mood Measures Within CN, sd-aMCI, and LOD Groups

		GDS	State-Trait Anxiety Inventory	DAS
CN	Positive bias	0.34	0.02	−0.64
	Significance (p)	0.20	0.95	0.008
	Negative bias	−0.04	0.09	−0.32
	Significance (p)	0.89	0.73	0.23
sd-aMCI	Positive bias	0.02	−0.10	−0.57
	Significance (p)	0.93	0.70	0.02
	Negative bias	−0.15	0.09	−0.39
	Significance (p)	0.59	0.73	0.14
LOD	Positive bias	0.05	−0.19	−0.24
	Significance (p)	0.86	0.48	0.36
	Negative bias	0.13	−0.30	−0.20
	Significance (p)	0.62	0.25	0.45

Notes: Values in table represent Spearman's rho (r_s) with significance level below.

FIGURE 1. Group differences in EEM. Cognitively normal adults demonstrate a positive emotional memory bias (calculated as the difference between number of emotionally valenced and neutral words recalled: Pos-EEM = POS-recall-NEU-recall); aMCI and LOD groups demonstrate a negative emotional bias (Neg-EEM = NEG-recall-NEU-recall). Error bars are standard error of the mean.



Similarly, Pos-EEM and DAS were inversely correlated in sd-aMCI participants ($r_s = –0.57$, $p = 0.02$), but this was not significant after correction for multiple comparisons. No other correlations were significant.

Associations between EEM and Executive Function

Neg-EEM and the Card Sorting Task[b] were inversely correlated in CN adults ($r_s = –0.87$, $p = 0.001$, $n = 10$) and remained statistically significant after correction for multiple comparisons (Table 5). In sd-aMCI participants, Pos-EEM was moderately correlated with FAS letter fluency ($r_s = 0.50$, $p = 0.047$), whereas Neg-EEM was directly correlated with the Trail Making Test-B[c] and the Stroop Color-Word Test ($r_s = 0.56$, $p = 0.037$ and $r_s = 0.48$, $p = 0.06$, respectively) and inversely correlated with the Card Sorting Task ($r_s = 0.–44$, $p = 0.099$). None of these correlations were significant after correction for multiple comparisons. Similar but nonsignificant patterns of better executive function and greater Pos-EEM/decreased Neg-EEM were observed in the LOD group.

DISCUSSION

The purpose of this study was to compare emotional memory among sd-aMCI, LOD, and CN adults using a novel EVeLT task that required wordlist learning of positive, negative, and neutral personality adjectives. As hypothesized, Neg-EEM was observed in sd-aMCI and LOD groups, whereas Pos-EEM was found in CN adults. Pos-EEM was associated with reduced tendency to endorse negative attitudes regarding self in CN adults and to a lesser extent in sd-aMCI adults. Exploratory analyses suggested an overall pattern of an association between better executive function and decreased Neg-EEM/increased Pos-EEM in sd-aMCI and CN participants. No significant correlations between EEM and mood or executive function were found in LOD participants. To the best of our knowledge, this is the first study to report alterations in emotional memory specific to sd-aMCI and LOD.

Although negatively biased emotional processing has been reported in depression in late life, it has been unclear whether it is evident in LOD, because studies have typically included mixed samples of early- and

[b]Card Sorting Task data available for 10 of 16 CN participants.
[c]Trail Making Test-B data available for 15 of 16 sd-aMCI participants.

TABLE 5. Correlations Between Emotional Bias Memory Scores and Executive Function Measures within CN, sd-aMCI, and LOD Groups

		Trail Making Test-B[a]	Stroop Color-Word Test[b]	FAS Letter Fluency	Card Sorting Task[c]
CN	Positive bias	−0.13	−0.14	0.02	−0.48
	Significance (p)	0.62	0.64	0.94	0.16
	Negative bias	0.22	−0.001	−0.27	−0.87
	Significance (p)	0.42	1.00	0.32	0.001
sd-aMCI	Positive bias	0.23	0.38	0.50	−0.21
	Significance (p)	0.43	0.15	0.047	0.44
	Negative bias	0.56	0.48	0.07	−0.44
	Significance (p)	0.04	0.06	0.81	0.10
LOD	Positive bias	−0.13	−0.38	0.45	−0.23
	Significance (p)	0.67	0.18	0.12	0.46
	Negative bias	0.43	0.04	−0.33	−0.19
	Significance (p)	0.12	0.90	0.27	0.53

Notes: Values in table represent Spearman's rho (r_s) with significance level below. Trail Making Test-B: time needed to complete task; higher number indicates poorer executive function. Stroop Color-Word test: time needed to complete task; higher number indicates poorer executive function. FAS Letter Fluency: number of correct responses; higher number indicates better executive function. Card Sorting Task: number of correct categories; higher number indicates better executive function.

[a]Data missing for 1 sd-aMCI and 2 LOD participants.

[b]Data missing for 2 CN and 2 LOD participants.

[c]Data missing for 5 CN and 2 LOD participants.

late-onset depression.[10,11,13,15,17] Although no differences in judgments of word valence were found between LOD and CN older adults in a functional magnetic resonance imaging,[6] our findings in LOD suggest that later stages of information processing (i.e., encoding and retrieval) may be influenced by emotional valence.

Our findings of Neg-EEM in sd-aMCI extend previous reports of negatively biased emotional working memory[30] and biased recall for depression-relevant words in MCI compared with CN adults[24] but contradict other studies of emotional wordlist learning in MCI that suggested no alterations in EEM.[22,24,26] It is unlikely that subsyndromal depressive symptoms account for the Neg-EEM observed in sd-aMCI participants, given their nonelevated depression or anxiety scores.

Why did we observe negative EEM in sd-aMCI participants but other studies failed to report differences in EEM between MCI and CN adults? This may be attributable to sample characteristics, task or stimulus features, or both. Our sample was restricted to single-domain aMCI participants who were carefully screened to exclude those with cognitive impairment due to psychiatric illness. We are not aware of any previous studies of EEM that focused only on sd-aMCI. This strategy likely resulted in a more cognitively homogeneous group than samples of mixed sd-aMCI and multidomain aMCI, allowing us to detect subtle group differences in EEM. It is also possible that EEM is altered according to disease progression; for example, absence of EEM (no enhanced recall of positive or negative information over neutral) appears to characterize advanced AD.[51] Neg-EEM may be found only in the earliest stages of preclinical AD. This hypothesis could be tested by comparing emotional memory at various stages of AD (e.g., sd-aMCI, md-aMCI, mild AD).

A key methodologic difference between the current and previous EEM work in MCI[24] is that our task presented positive, negative, and neutral words pseudo-randomly ordered in a single list. EEM is more likely to be detected when emotional and neutral stimuli are presented together as opposed to separate lists according to valence,[32] a phenomenon explained by arousal-based competition models of attention and memory consolidation. The competition model suggests that under conditions of constrained attention (e.g., words are presented quickly), salient, highly arousing, and frequently, negatively valenced, information is more likely to be attended to and recalled, relative to competing neutral stimuli.[52] Thus, the effects of emotional valence on attention or memory are accentuated during mixed-valence wordlist learning, whereas there is no competition for attention by valence in lists that include only words of the same valence. The competition model

implies that cognitive control should impact on EEM. There is evidence of an age-related association between executive function and positivity[53–58] (but see Foster et al.[59] for conflicting findings). In particular, it has been hypothesized that older adults may rely on cognitive control to selectively focus on positive and ignore negative stimuli.[55,60] Our findings of positive EEM and the inverse associations between executive function and negative EEM in CN participants provide further support for the notion of enhanced cognitive control as a potential mechanism for the positivity bias observed in older adults.[9] The Neg-EEM observed in sd-aMCI may result from impaired cognitive control over emotions, or emotion dysregulation, as a consequence of pathologic changes in regions such as the ventral anterior cingulate cortex that regulate the amygdala.[3,8] This hypothesis could be tested using emotion regulation task paradigms and functional neuroimaging in sd-aMCI.

With regard to stimulus features, use of personality adjectives rather than nouns may have invited subjects to engage in a self-referential strategy during encoding, although not explicitly instructed to do so. This hypothesis is suggested by the strong inverse association between memory for positive personality traits and negative attitudes regarding self, observed in the CN group and to a lesser extent in sd-aMCI participants. It is well established that memory is enhanced when information is processed with reference to self (i.e., the "self-reference" effect on memory).[61] The self-reference effect has been observed in healthy individuals and also in AD. In a study of healthy young and older adults, the positivity effect in the older age group was enhanced when participants were asked to recall emotion stimuli that were self-relevant.[57] Similarly, CN participants recalled more positive and neutral words under self-referential, as opposed to semantic, encoding conditions. This was not observed in AD participants, who instead showed an increase in recall of negative words in the self-referential condition, suggesting that the self-reference effect enhanced negative EEM specifically in AD.[62]

Contrary to predictions, mood and anxiety symptoms did not correlate with EEM, even in the LOD group, who instead showed similar but nonsignificant associations between executive function and EEM. The failure to detect a relationship between EEM and mood or executive function may be attributable to greater heterogeneity in the etiology of LOD, which may be vascular- or cortisol-mediated,[63] together with the relatively small sample sizes and missing executive measures.

Our observed Neg-EEM in aMCI appears to contradict a recently published study that reported Pos-EEM in aMCI on incidental recall of visually presented words with positive, negative, or neutral valences.[15] In this study, participants in one of four groups (aMCI with depressive symptoms, aMCI without depressive symptoms, late-life depression, or CN) were instructed to rate the valence of words without being informed a memory test would follow. If Hochberg's step-up correction for multiple comparisons is applied, CN adults showed a Pos-EEM and Neg-EEM, both aMCI groups (±depression) showed a Pos-EEM, and no valence effects were found in the late-life depression group. Although direct group comparisons were not performed, the study suggests aMCI may show Pos-EEM in incidental recall of information. We postulate that aMCI participants may exhibit Pos-EEM when performing tasks that require minimal cognitive effort, but cognitively taxing tasks (i.e., explicit instructions to remember words) reduce their ability to downregulate responses toward, or ignore, negative information. This hypothesis is compatible with the healthy aging literature suggesting that the magnitude of the positivity bias is greater when information processing is less constrained by cognitive demands of the task.[64] Future work should compare incidental and explicit recall of emotionally valenced information in aMCI.

Strengths of the current study include our novel task of emotional memory and the well-characterized sd-aMCI, LOD, and CN groups using neuropsychological and neuropsychiatric assessments. Weaknesses include small sample sizes, which may explain the failure to detect statistically significant associations between EEM and cognition in LOD. Another important consideration is that by studying sd-aMCI participants, the underlying etiology of the memory impairment may be more heterogeneous compared with multidomain aMCI samples, who are at greater risk for AD than sd-aMCI[33,65,66] (but see Yaffe et al.).[34] Nevertheless, our findings suggest the hypothesis that the earliest stages of AD may be characterized by impaired emotion regulation as a consequence of neuropathologic disruption of limbic structures and networks. This hypothesis is compatible with the epidemiologic associations between neuropsychiatric symptoms such as depression and

anxiety and AD risk.[18,67] Given that disease-modifying interventions for AD may be more effective in the presymptomatic stages of AD, our findings of negative EEM in sd-aMCI and LOD support the need for longitudinal studies and inclusion of AD biomarkers to examine emotional processing as a means to characterize, and potentially identify, individuals in the preclinical phase of AD.

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