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Differential prefrontal and subcortical circuitry engagement during encoding of semantically related words in patients with late-life depression

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Objective: Verbal memory difficulties are common among individuals with late-life depression (LLD), though there is limited knowledge about disruptions to underlying cerebral circuitry. The purpose of this study is to examine aberrations to cerebral networks implicated in encoding novel verbal semantic material among older adults with LLD.

Methods: Twenty-four older adults with early-onset LLD and 23 non-depressed comparisons participated in the study. Participants completed a word list-learning task while undergoing functional magnetic resonance imaging.

Results: In the context of equivalent recall and recognition of words following scanning and similar hippocampal volumes, patients with LLD exhibited less activation in structures known to be relevant for new learning and memory, including hippocampus, parahippocampal gyrus, insula, and cingulate, relative to non-ill comparisons. An important region in which the LLD group displayed greater activation than the non-depressed comparison group was in left inferior frontal gyrus, an area involved in cognitive control and controlled semantic/phonological retrieval and analysis; this region may be critical for LLD patients to consolidate encoded words into memory.

Conclusions: Functional irregularities found in LLD patients may reflect different modes of processing to-be-remembered information and/or early changes predictive of incipient cognitive decline. Future studies might consider mechanisms that could contribute to these functional differences, including hypothalamic-pituitary-adrenal axis functioning and vascular integrity, and utilize longitudinal designs in order to understand whether functional changes are predictive of incipient cognitive decline.

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Introduction

Neuropsychological impairment has been documented in older adults with major depressive disorder (MDD) across domains, and especially in the areas of episodic memory, processing speed, and executive function (Elderkin-Thompson *et al.*, 2007; Yen *et al.*, 2011; Lamar *et al.*, 2012; Dybedal *et al.*, 2013). Although neuroimaging research has primarily focused on the role of executive functioning in late-life depression (LLD; e.g., Aizenstein *et al.*, 2009; Alexopoulos *et al.*, 2012), individuals with LLD also frequently exhibit poor memory on objective neuropsychological measures (Dillon *et al.*, 2011).

There are multiple hypotheses for why individuals with LLD would experience memory loss. Structural magnetic resonance imaging (MRI) studies have demonstrated lower hippocampal volume among

older patients with MDD (Zhao *et al.*, 2008; Steffens *et al.*, 2011). Depressed individuals with and without objective memory loss have also demonstrated altered hippocampal resting state functional MRI (fMRI) connectivity with prefrontal regions and posterior cingulate (Xie *et al.*, 2013). Early memory deficits in may be a warning sign of impending cognitive decline, as LLD is associated with LLD an increased risk of developing dementia (Ownby *et al.*, 2006; Diniz *et al.*, 2013). As most cognitive and neuroimaging studies of LLD are not longitudinal, it is not clear what markers might suggest future decline and/or dementia. Data suggest that cerebral functional changes often appear before demonstrable behavioral changes (Forsberg *et al.*, 2008; Park *et al.*, 2012; Fujishiro *et al.*, 2013; see Risacher and Saykin, 2013) and may serve as a marker for continuing cognitive decline or functional impairment, making development of sensitive functional probes imperative.

To this end, task-based functional MRI methodology, primarily in executive functioning abilities, has been applied in order to better understand cerebral abnormalities among older patients with LLD (e.g., Aizenstein *et al.*, 2009; Alexopoulos *et al.*, 2012; Dybedal *et al.*, 2013). Executive functioning can play a significant role in supporting memory processes, and measures of memory often include significant contributions from executive functioning components. For example, list-learning tasks such as the California Verbal Learning Test-2 (CVLT; Delis *et al.*, 2000) uses words from distinct semantic categories. If detected by the participant, the semantic categories offer a clustering or "chunking" strategy to increase encoding efficiency (Winocur and Moscovitch, 2011). Executive functioning drives discernment to the lists' semantic organization and utilization of the clustering strategy; as a result, variance in executive functioning skill impacts how much is remembered. As memory and executive functioning processes are often intertwined, it is difficult to parse out the relative contributions of executive functioning and memory processes. Memory tasks that exclude strong executive functioning contributions may be sensitive for identifying those early in the course of memory decline or in pinpointing specific functional impairments. For example, a study of LLD adults reported that impairment in semantic organization mediates performance on the CVLT and is absent in non-depressed older adults (Elderkin-Thompson *et al.*, 2007).

To our knowledge, there have been no functional imaging studies in LLD that use recall-based memory tasks with diminished contributions from executive functioning circuits. In the current study, we use the Semantic List Learning Test (SLLT), in which lists of words are presented with semantic category labels, reducing the necessity for subjects to generate their own organizational strategies for encoding words. It also utilizes a Brown-Peterson paradigm, such that a distractor task is presented immediately following encoding in order to reduce the ability of subjects to use short-term-memory stores (a frontally mediated process) to augment weaker primary memory. The SLLT also allows for objective examination of memory performance, as it includes paper-and-pencil recall and recognition assessments immediately following scanning. We included only patients in this study with first onset of depression <55 due to possible etiological differences between early and late-onset LLD (Murata *et al.*, 2001; Sachs-Ericsson *et al.*, 2013) and to minimize the likelihood of other medical processes (i.e., cardiovascular and metabolic processes) contributing to disease pathogenesis. We hypothesized that LLD adults would demonstrate poorer performance on the SLLT relative to non-depressed comparison adults (NDC) and that LLD adults would demonstrate BOLD fMRI abnormalities in regions relevant to memory encoding and consolidation (Papez, 1937).

Methods

Participants

This study was approved by the Institutional Review Board at the University of Michigan, and all participants gave informed consent prior to participation. Forty-seven participants (24 LLD, 23 NDC) were recruited through geriatric psychiatry and primary care clinics, clinical research volunteer databases, and community advertisements. One additional subject was excluded due to significant atrophy observed on the anatomical scan and a second subject was excluded due to significant dorsal section of the brain missing from functional scans. Exclusionary criteria for all participants included contraindications for MRI, mini-mental state exam <24 (O'Bryant *et al.*, 2008), uncontrolled hypertension or diabetes, any neurological disorder, head injury with loss of consciousness of >5 min, and major medical conditions that could affect the central nervous system. Participants were also excluded based upon any history of psychotic symptoms, bipolar disorder, schizophrenia, current substance use disorder, or history of substance dependence within 5 years of the MRI scan. All LLD participants had age of depression onset <55 years old. Individuals were not excluded on the basis of taking psychotropic medications, although those with

PRN anxiolytic usage were encouraged to avoid use on the day of the scan. NDC participants were free from a personal history of psychiatric illness. All LLD participants were diagnosed according to the structured clinical interview for the DSM-IV criteria (Spitzer *et al.*, 1994). Depression severity was measured with the Hamilton Rating Scale for Depression–Second Edition (Hamilton, 1967). It is relevant to note that participants were not experiencing overt memory deficits at the time of recruitment and testing, and performance on the CVLT was not utilized as part of inclusion/exclusion criteria. CVLT data were available for 21 participants in each group, and the average age-corrected z-scores for recognition in each group were within the normal range. One NDC and four LLD participants achieved a score that was at least 1.5 standard deviations below the age-corrected mean for long delay free recall. Table 1 lists specific demographic, cognitive, and medical characteristics for the sample.

Measures

The SLLT, designed to test learning and memory, is composed of three types of blocks that were presented during fMRI scanning: encoding, distraction, and silent rehearsal (Figure 1).

Table 1 Sample demographic and clinical characteristics

	LLD ($n = 24$)	NDC ($n = 23$)
Variables	*M* (*SD*)	*M* (*SD*)
Age	65.8 (8.2)	67.9 (8.1)
Education	15.9 (2.7)	16.7 (2.1)
Sex (female *n*)	14	10
Hamilton Depression Rating Scale[a]	15.71 (5.2)	0.96 (1.0)
Charlson Comorbidity Index	0.24 (0.49)	0.1 (0.34)
CVLT-2 Delayed Recall Z-Score[b]	0.10 (1.1)	0.52 (1.0)
Years of illness[c] (MDD only)	39.8 (16.8)	NA
On psychotropic medication[d] (%)	78	NA
Diabetes (*n*)	0	3
Hypertension (*n*)	11	6
Sleep apnea (*n*)	2	1
Heart condition (*n*)	5	2
Anemia	2	0

LLD, late-life depression; NDC, non-depressed comparison; CVLT-2, California Verbal Learning Test-2; MDD, major depressive disorder.
[a]$t(45) = -13.64$, $p < 0.001$.
[b]$n = 21$ per group.
[c]Years ill missing for one subject.
[d]Medication status missing for one LLD; one NDC subject was taking trazadone for sleep. Of the participants with LLD, 22% ($n = 5$) were unmedicated, 30% ($n = 7$) were taking SSRI/SNRI only, 30% ($n = 7$) were taking SSRI/SNRI in addition to another psychoactive medication (e.g., bupropion, trazodone, and benzodiazepine), 13% ($n = 3$) were taking non-SSRI/SNRI antidepressants (i.e., trazodone, bupropion, and gabapentin), and one participated was taking a benzodiazepine (PRN) only.

Subjects were presented with 14 words from one of 15 semantic categories during each encoding block. Lists were taken from word category and frequency work by Winograd (1968), with five of each low, medium, and high frequency categories. Lists were respectively matched for average number of syllables, and categories had sufficient items for both within list targets and same list distractors (for the recognition part of the task). In the task, a prompt with the name of the semantic category being studied was displayed for 3.5 seconds. Words from that category were then presented for one second each with a one to four second jittered inter-stimulus interval, during which a fixation cross was presented. The total time for each encoding block was 58.25 s. Subjects then completed a serial stream "Go" distractor task for 14 s where they responded to letters x, y, and z. This was intended to reduce recency effects during recall/recognition by preventing rehearsal of list items held in short-term memory (Brown, 1958; Peterson and Peterson, 1959). The final portion of each list presentation consisted of a silent rehearsal block that lasted for 14 s. Here, participants saw the category prompt and were asked to silently rehearse words that were just presented during the previous encoding phase. Participants were presented with a total of 15 different word lists over five runs (three lists per run), for a total of 210 words. All participants were presented with the same word lists, but the order of each of three lists within a given run, and of each word within a list, were randomized. At the end of each of the five runs, there was a rest period of 32 s.

Procedure

Participants were verbally introduced to the task by the experimenter prior to entering the scanner. They were told they would observe lists of categorically related words presented one at a time and that they should silently read and remember the words to the best of their ability, utilizing the list category as a semantic encoding strategy. They were informed that a different (distractor) task would then appear for which they had to make a button-press response each time they saw the letters "x," "y," or "z" presented in a visual stream, on which participants were trained prior to scanning. Lastly, they were told that a silent rehearsal phase would occur, during which they would be asked to rehearse the words from the list that appeared just prior to the distraction phase without vocalization or movement of the lips.

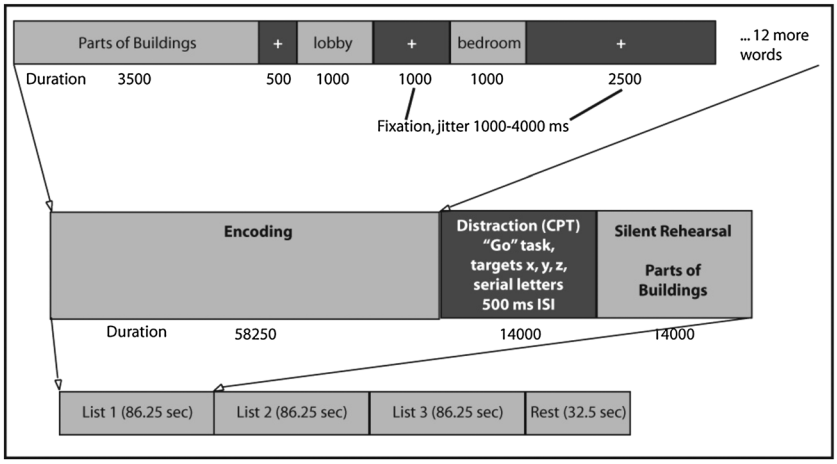

Figure 1 Illustration of semantic list learning test. Participants are presented with 15 lists of 14 semantically related words (210 words total). Each list is preceded by its Semantic List Learning Test. A period of instructed silent rehearsal follows a distractor task after each list in the functional magnetic resonance imaging scanner, whereas free recall is conducted upon completion of the scanning session, outside of the scanner.

After scanning, subjects first completed a recall task in which they wrote down all the words they could remember for each of the semantic categories presented. Category name prompts were provided as recall cues. Subjects then completed a recognition task in which they had to discern words seen inside the scanner from a list of correct words among semantically related and unrelated distractors. Distractors made up approximately 46% of the words in the recognition task. Correctly recalled words and those that were not recalled were used as regressors in an event-related analysis of the fMRI data. Correctly recognized words and those that were not recognized were used in the same manner.

Functional MRI procedures were similar in detail and followed the method used in our previous work (e.g., Langenecker *et al.*, 2007; Langenecker *et al.*, 2012; Weisenbach *et al.*, 2014; see supplementary material). High-resolution T_1 spoiled gradient (SPGR) anatomical images (echo time = 3.4 ms, repetition time = 10.5 ms, 27° flip angle, number of excitations = 1, slice thickness = 1.5 mm, field of view = 24 cm, matrix size = 256 × 256) were obtained after SLLT administration and used in voxel-based morphometry analyses. To assure that any between-group differences were not due to atrophy in the LLD group, we utilized voxel-based morphometry (VBM). Given the relevance of the hippocampus to memory encoding, we first tested for differences in hippocampal volume by creating a hippocampal region of interest (ROI) using the WakeForest PickAtlas (Maldjian *et al.*, 2003). We conducted additional VBM analyses of functional regions found to be significantly different between the two groups by creating masks of these regions using the REST program (Song *et al.*, 2011). VBM analyses were conducted with the VBM8 toolbox in SPM8 (Kurth *et al.*, 2010).

Statistical analyses

Behavioral data were examined using *t*-tests and employed a statistical threshold of $p < 0.05$. We investigated group differences in recall hits, recall false positives, recognition hits, recognition false positives, d′ (a sensitivity index that provides the separation between means of the signal and noise distributions, compared against the standard deviation of the noise distribution), and β (a measure of response bias). In calculating d′ and β for recall, total number of possibly recognized items was used to generate the false alarm rate. There was one outlier in the NDC group for recognition false positive errors, and this was winsorized so that it was equivalent to the next most poorly performing person within the NDC group. For VBM analyses, a two-sample *t*-test was performed to assess for group differences in hippocampal volume and functional regions found to be significantly different between the NDC and LLD groups. To assure that volumetric differences of relevant regions were minimal between the two groups, we employed a liberal threshold of $p < 0.05$, minimum threshold cluster of 80 mm^3 for all VBM analyses. Functional images were normalized to fit a Montreal Neurological Institute canonical template and were smoothed at a 5 mm FWHM. For fMRI data, three contrasts of interest were run. First, word encoding blocks were compared with silent rehearsal blocks. Second,

event-related encoding of correctly recalled words were compared with non-recalled words, as well as the inverse (encoding of non-recalled compared to recalled words; see Supplemental Material). Finally, we tested event-related recognized words compared with not recognized words, as well as the inverse (encoding of non-recognized compared with recognized words; see Supplemental Material). Group analyses with *t*-tests were conducted with these contrasts, run in SPM8. AlphaSim (Ward, 2000) correction (1000 iterations) was used for all whole brain analyses, balancing height ($p < 0.003$) and extent ($264\,mm^3$) thresholds to achieve a whole brain correction of $p < 0.05$. For the hippocampal ROI analysis, a threshold of $p < 0.05$, $80\,mm^3$ was utilized. In a *post hoc* analysis of activation in the left inferior frontal gyrus (IFG), the MarsBaR toolbox (Brett *et al.*, 2002) was used to extract mean signal change in IFG ROI for correlation with performance measures of recall, recognition, d′, and β. All fMRI analyses were performed with and without the inclusion of the five individuals with poor CVLT performance.

Results

Group comparisons for cognitive performance. The LLD and NDC groups did not differ in performance for recall hits, recall false positive errors, recognition hits, recognition false positive errors, d′ or β (all $ps > 0.31$; see Figure 2(a) and (b).

Voxel-based morphometry. Hippocampal volume, corrected for whole brain volume, was not significantly different between LLD and NDC. The volumes of functional regions found to be significantly different between the two groups were also not significantly different in size between LLD and NDC.

Functional magnetic resonance imaging activation during encoding minus rehearsal of words. Late-life depression activation for encoding-rehearsal foci are listed in Table 2 as is NDC activation. Relative to LLD, greater activation was found in NDC in right middle frontal, insula, cuneus, and caudate, left dorsal cingulate, precuneus and putamen, and bilateral globus pallidus. LLD did not activate any region to a significantly greater degree than NDC. Table 2 and Figure 3 display regions activated in each of LLD and NDC separately and in NDC minus LLD contrast, both for whole brain and hippocampal ROI analyses. After removing the five participants with poor CVLT performance, similar between-group differences were detected in frontal and subcortical regions. Differences in insula, cuneus, and globus pallidus were no longer significant, and there were additional activation differences in left IFG and right postcentral gyrus and claustrum (Table S2(a)).

Activation during encoding of recalled versus not recalled words. During encoding of correctly recalled versus not recalled words, LLD activated left dorsal anterior cingulate, while NDC activated left medial frontal gyrus. NDC activated left caudate and left medial frontal gyrus to a greater degree than did LLD, who did not activate any area to a greater degree than did NDC (Table 3, Figure 4). When the five individuals with poor CVLT performance were removed, LLD displayed additional activation in left IFG, and group differences in activation disappeared (Table S2(b)).

Activation during encoding of recognized versus not recognized words. During encoding of correctly recognized versus not recognized words, LLD activated a number of frontal regions (left medial and right middle frontal and bilateral IFG and

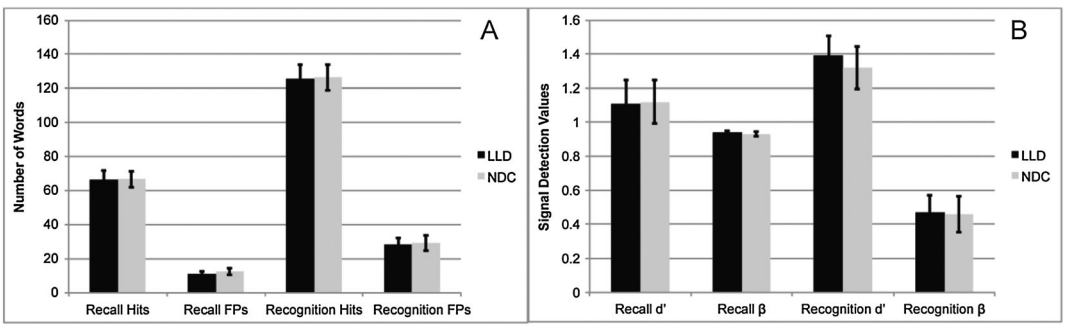

Figure 2 Performance during recall and recognition tasks. (a) Equivalent performance for recall hits and false positive (FP) errors and recognition hits and FP errors (all $ps > 0.31$). (b) Equivalent performance for recall and recognition d′ and β (all $ps > 0.64$).

Table 2 Foci of significant activation for encoding minus rehearsal

Group	Lobe	Region	BA	MNI coordinates			Z	mm^3
				x	y	z		
LLD	Frontal	Dorsal anterior cingulate[b]	32	10	22	27	5.28	23,352
		Middle frontal[b]	6	−31	−3	40	4.4	6464
		Anterior cingulate[b]	24	24	−3	44	4.1	2392
	Temporal	Insula[b]	13	40	30	19	3.8	1960
			13	45	−40	31	3.2	320
	Occipital	Inferior occipital	19	−46	−70	−2	4.0	1248
	Subcortical	Cerebellum-declive[b]	—	10	−75	−13	7.2	167,200
		Thalamus[b]	—	−17	−19	15	5.3	20,128
		Putamen[b]	—	−25	22	3	3.6	2344
NDC	Frontal	Inferior frontal	47	17	28	−13	3.8	1272
		Dorsal cingulate[b]	31	−10	−21	43	3.2	456
	Temporal	Superior temporal	38	−36	8	−24	4.1	600
			38	−31	12	−33	3.8	512
NDC	Temporal	Superior temporal	38	36	12	−26	4.1	400
	Parietal	Posterior cingulate	31	24	−17	48	4.9	3128
			31	15	−38	49	3.9	1496
		Postcentral[b]	3	−32	−25	41	3.6	1384
		Precuneus	7	−13	−38	56	3.4	952
	Occipital	Fusiform	19	45	−67	−9	5.0	3128
			19	−38	−71	−7	4.8	1632
			18	−25	−91	−16	4.7	1392
	Subcortical	Putamen[b]	—	−15	8	−10	3.5	608
			—	36	−1	8	3.9	480
		Caudate head[b]	—	4	8	5	3.7	312
		Hippocampus[a]	—	26	−17	−17	2.2	144
NDC-LLD	Frontal	Middle frontal	6	26	−6	60	4.0	1680
		Dorsal cingulate	24	−20	−14	50	3.7	1120
	Temporal	Insula[b]	13	38	16	−8	3.5	744
NDC-LLD	Temporal	Insula[b]	13	44	14	2	3.3	376
	Parietal	Precuneus[b]	7	−16	−38	54	3.2	304
	Occipital	Cuneus[b]	18	24	−92	26	3.7	344
	Subcortical	Caudate	—	16	−4	20	3.9	1608
		Lateral globus pallidus[b]	—	−22	8	6	3.1	360
			—	26	−12	8	3.9	312
		Putamen	—	−20	6	12	3.3	360

LLD, late-life depression; NDC, non-depressed comparison; MNI, Montreal Neurological Institute.
[a]Indicates hippocampal region of interest analysis at $p < 0.05$
[b]Indicates regions that were no longer significant after ($n = 5$) individuals with poor California Verbal Learning Test performance were removed.

precentral gyri), as well as left fusiform gyrus, right thalamus/mammillary body, putamen, and uvula, and bilateral parahippocampal gyrus, while NDC activated only right fusiform gyrus and hippocampus and left parahippocampal gyrus. In group comparisons, LLD activated left IFG to a significantly greater degree than did NDC, while NDC activated left superior temporal and right middle occipital gyri and hippocampus to a greater degree than did LLD (Table 4, Figure 5). When the five individuals with poor CVLT performance were removed from analysis, the LLD group demonstrated some notable differences in patterns of activation, as listed in Table 4 and Table S2(c). In group comparisons, LLD still demonstrated greater left IFG activation than NDC, though NDC demonstrated greater activation only in right middle occipital gyrus (Table 4).

Relationships of inferior frontal gyrus activation to performance (Figure 5). Late-life depression activated only one region (IFG) to a greater extent than did NDC, in the context of preserved performance. Values in this region were extracted (MarsBaR) during each of the three aforementioned contrasts, in order to understand whether there were any relationships with performance (compensation/interference). Bivariate Pearson correlations were conducted in each group separately, and the entire sample; IFG activation, recall hits and false positive errors, recall d′, and recall β, as well as recognition hits and false positive errors, recognition d′, and recognition β. One significant relationship was observed in LLD only, with a negative relationship between recall false positives and activation in IFG ($r = -0.44$, $p = 0.03$). One LLD individual had a large number of recall false positives and after

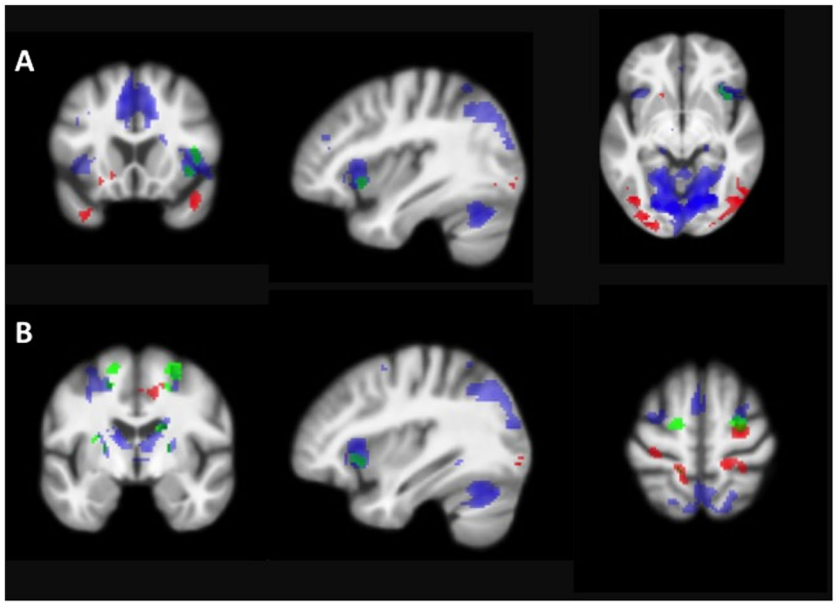

Figure 3 Activation during encoding versus rehearsal. Panels A (38 16–8) and B (36–6 60) illustrate statistically significant activation in areas for the late-life depression (LLD) group (blue), the non-depressed comparison (NDC) group (red), and the NDC minus LLD contrast (green).

Table 3 Foci of significant activation for Recalled versus Not Recalled Words

				MNI coordinates				
Group	Lobe	Region	BA	x	y	z	Z	mm^3
LLD	Frontal	Dorsal anterior cingulate	32	−2	14	50	3.8	584
NDC	Frontal	Medial frontal[a]	11	−8	56	−14	3.6	480
NDC-LLD	Frontal	Medial frontal	10	−6	56	−12	3.8	272
	Subcortical	Caudate[a]	—	−40	−22	−2	3.3	272

LLD, late-life depression; NDC, non-depressed comparison; MNI, Montreal Neurological Institute.
[a]Indicates regions that were no longer significant after ($n = 5$) individuals with poor California Verbal Learning Test performance were removed.

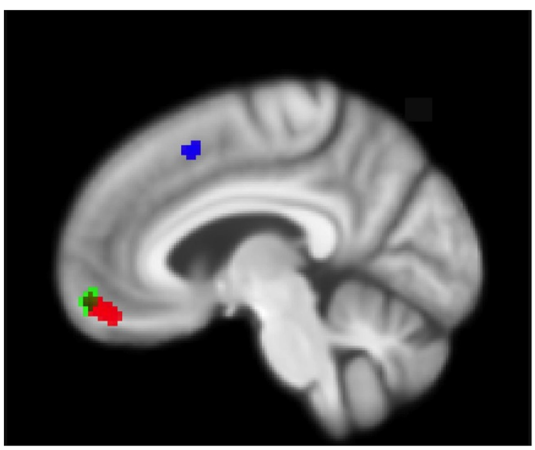

Figure 4 Activation during encoding of recalled versus not recalled words. Illustrates medial frontal regions that are statistically significant in the late-life depression (LLD) group (blue), the non-depressed comparison (NDC) group (red), and NDC greater than LLD (green; −6 56–12).

truncation of that outlier, the correlation was no longer significant ($r = -0.12$, $p = 0.57$). Results were the same after individuals with poor CVLT performance ($n = 5$) were removed from analysis.

Discussion

This study considers the impact of LLD upon memory and supportive neural circuits. Patients with LLD exhibit less activation in structures known to be relevant for new learning and memory, relative to NDC, despite performing at similar levels on a word-list learning and memory task and having equivalent hippocampal volumes. This phenomenon was observed on a task specifically designed to minimize individual differences in the contribution of executive functioning to memory performance and is present in

Table 4 Foci of significant activation for recognized versus not recognized words

Group	Lobe	Region	BA	MNI coordinates x	y	z	Z	mm^3
LLD	Frontal	Dorsal anterior cingulate[b]	32	−2	14	50	4.9	6680
		Inferior frontal	45	−48	22	14	4.5	3632
			47	40	20	−6	3.3	360
		Middle frontal	46	44	22	26	4.6	2624
		Precentral[b]	6	−32	8	28	4.6	2584
			6	38	−4	38	4.1	344
	Temporal	Fusiform[b]	37	−48	−50	−14	3.9	528
	Subcortical	Thalamus/mammillary body[b]	—	12	−16	2	3.3	800
		Putamen[b]	—	32	−2	12	4.1	584
			—	22	2	14	4.2	304
		Parahippocampal gyrus[a, b]	36	−32	−14	−22	2.2	168
			28	26	−12	−22	2.5	104
	Cerebellum	Uvula[b]	—	10	−74	−32	3.7	400
NDC	Temporal	Fusiform	20	56	−30	−22	3.3	360
	Subcortical	Hippocampus[a]	—	30	−14	−16	2.7	136
		Parahippocampal gyrus[a]	36	−28	−40	−2	2.2	128
LLD-NDC	Frontal	Inferior frontal	45	−48	22	14	3.7	440
NDC-LLD	Temporal	Superior temporal[b]	39	−55	−60	9	3.3	544
	Occipital	Middle occipital	19	47	−73	8	3.4	280
	Subcortical	Hippocampus[a, b]	—	32	−16	−14	2.6	120

LLD, late-life depression; NDC, non-depressed comparison; MNI, Montreal Neurological Institute.
[a]Indicates hippocampal region of interest analysis at $p < 0.05$
[b]Indicates regions that were no longer significant after ($n = 5$) individuals with poor California Verbal Learning Test performance were removed.

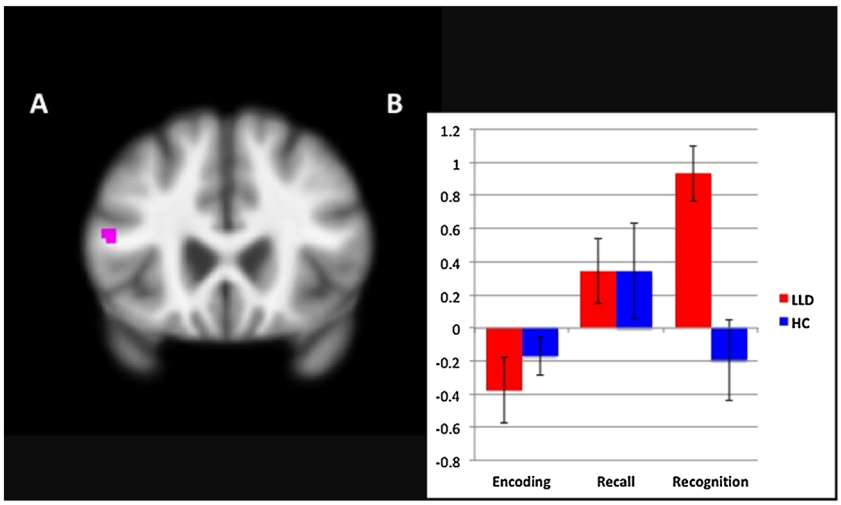

Figure 5 Greater activation in inferior frontal gyrus in late-life depression (LLD) during encoding of recognized versus not recognized words. (a) Activation of inferior frontal gyrus greater in LLD than non-depressed comparison (−68 22 14). (b) Mean extracted activation values from the IFG in each group during encoding minus rehearsal, encoding of recalled versus not recalled words, and encoding of recognized versus not recognized words, respectively. Note. All images displayed on a mean anatomical brain of the entire sample.

individuals with LLD who, as a whole, do not have objective memory difficulties on standard clinical measures. Findings suggest that these neuroimaging measures potentially provide more sensitive markers of dysfunction, present before they are detected in standard neuropsychological batteries.

This older NDC sample exhibited activation during encoding (relative to rehearsal) of novel verbal items in regions known to be important in verbal learning and memory, including prefrontal cortex and fusiform gyrus (content processing), hippocampus (storage), and parietal regions (attention; see Kim, 2011).

The largest areas of activation for LLD were in dorsal cingulate, middle frontal gyrus, thalamus, and cerebellum, potentially suggesting inefficiencies in loops that are most relevant for verbal memory, as well as the activation of networks thought to support executive functioning.

Given the functional differences observed in LLD relative to NDC, as well as the fact that the LLD group had experienced relatively large "doses" of depression over their lifetimes, it is surprising that performance differences (nor differences in anatomical volumes) were found between the two groups. A first possibility for this may be that functional changes often appear before structural and behavioral changes (Forsberg *et al.*, 2008; Park *et al.*, 2012; Fujishiro *et al.*, 2013; Risacher and Saykin, 2013). The sample included in this study was, by and large, functioning at a high capacity, without memory deficits, and were, by and large, still in the earlier years of older age. If we were to follow the LLD group longitudinally, however, those that display the greatest functional changes may also experience the most subsequent memory decline. A second possibility, and one that is supported by our findings (though not in conflict with the latter hypothesis proposed), is that LLD arrive at successful performance differently than do NDC. For example, the IFG appears to be critical for LLD patients to consolidate encoded words into memory, as reflected by correct recognition of words subsequent to scanning, but less so for NDC. Executive functioning problems are more frequently reported in LLD, and it is possible that compensatory mechanisms minimize the engagement of executive functioning (EF) circuits as a source of poor performance. Excluding those with overt memory or EF problems may have effectively limited the range of impairment in LLD in the present report. The IFG is an area involved in cognitive control (Tops and Boksem, 2011), language, and controlled semantic/phonological retrieval and analysis (Dobbins and Wagner, 2005; Badre and Wagner, 2007). While both groups utilized this region to a similar degree during encoding of subsequent correctly recalled words, LLD continue to do so to an even greater degree during encoding of correctly recognized words. LLD may be utilizing this as a compensatory region during encoding, potentially part of a process that is crucial for consolidation, or the subsequent inhibitory process of correctly rejecting words during the recognition trial. Moreover, the LLD group activated a far greater number of regions during encoding of correctly recognized words than did the NDC group, potentially reflecting the necessity of recruiting additional regions to assist with cognitive control processes. Compensatory processes observed during fMRI may signal the beginning stages of a neurodegenerative process, as has been observed in individuals in the early stages of mild cognitive impairment (e.g., Clément and Belleville, 2012). Alternatively, given that the IFG includes significant language processing regions, it is possible that greater activation in the LLD group is a reflection of greater subvocal rehearsal during the encoding phase. A third possibility is that the SLLT is too easy to reflect performance differences in an older depressed group. Literature suggests that actively depressed individuals tend to have the most difficulty with tasks that are more effortful (Hammar and Ardal, 2012). The SLLT is intentionally less complex and cognitively demanding for executive functioning skills than most typical verbal neuropsychological measures used in behavioral paradigms, such as the CVLT. These tasks require examinees to generate their own encoding strategy during the learning phase and retrieval strategy for the first part of recall. We further note that memory recall was typically somewhat low, at a mean of 31.6%, which would indicate that it is sufficiently difficult as a memory task. Furthermore, as we exclude MDD with significant cognitive impairment, introduction of arguments about null psychometric results can be thought of as tautological.

During encoding of correctly recalled words, both groups demonstrated activation of left medial frontal gyrus, albeit in different anatomical areas. Whereas LLD activated a dorsal region bordering on the anterior cingulate cortex, which is relevant to error detection (Orr and Hester, 2012), NDC displayed activation in a more ventral region thought to be crucial to self-referential processing (Yoshimura *et al.*, 2009). These findings again highlight the different processes by which LLD and NDC arrive at successful retrieval, with LLD perhaps utilizing a cognitive control strategy during encoding, and NDC possibly contextualizing to-be-remembered material to personal experiences. NDC also activated caudate and parahippocampal gyrus to a greater degree than did LLD during encoding of correctly recalled (versus not recalled) words. Recent evidence suggests that the caudate is crucial to goal-directed action selection (Ness and Beste, 2013) and has demonstrated greater activity following semantic encoding strategy training in older adults (Kirchhoff *et al.*, 2012). This may suggest that NDC in our sample utilized a more active encoding strategy than did LLD.

Despite a lack of group differences in performance and equivalent hippocampal volume, LLD demonstrate functional abnormalities during encoding of novel verbal material presented in a semantically organized fashion. It is important to note that all

LLD participants in this sample were classified as having early-onset depression (<55 years old), thought to be etiologically different from late-onset depression but similar in presentation from a phenomenological perspective (Grayson and Thomas, 2013). Furthermore, these depressed individuals were carefully screened to rule out any early dementia, rendering the sample a more conservative test of our hypotheses. Future research might consider mechanisms accounting for functional activation abnormalities in individuals with LLD, including hypothalamic-pituitary-adrenal axis functioning and cerebrovascular contributions, both widely researched in the depression literature.

It is important to note that when the five poor CVLT performers were removed from analysis, there were some changes in the pattern of activation, with generally greater activation being displayed in LLD and fewer between-group differences. This suggests that, while well performing patients still demonstrate abnormal activation patterns in regions relevant to learning and memory, the most abnormal patterns of activation are likely to be displayed in those with poorer memory functioning. While most studies of LLD exclude those with overt dementia, they usually include patients with a range of cognitive functioning. While the size of the sample in the current study precludes us from being able to make any strong conclusions in this regard, future studies might consider the contribution of cognitive status (i.e., those with and without mild cognitive impairment) to patterns of abnormal activation during cognitive challenge.

There are a few additional limitations that should be considered in interpreting results and generalizing findings to the wider population of individuals with LLD. First, our sample was highly educated and largely without objectively defined memory deficits. Results reflect functional abnormalities in memory processing pathways among non-cognitively impaired older adults with early-onset depression and may not generalize to those with subjective memory complaints, objectively defined memory problems, or onset of depression in late life. In regards to the latter, there is evidence to suggest that individuals with late-onset depression perform more poorly on cognitive measures than those with early-onset depression (Delaloye *et al.*, 2010; Sachs-Ericsson *et al.*, 2013). Thus, memory performance and disruption to pathways relevant for memory may be more apparent in a sample of individuals with late-onset depression. Because all patients were actively depressed, it is also not clear whether functional abnormalities represent state or trait effects of depression. Second, as this is not a longitudinal study, the extent to which findings of functional abnormalities might be indicative of incipient cognitive decline above and beyond LLD is unclear. Future studies might consider regions that were found to differ in functioning between groups as potential markers for investigation of prediction of cognitive decline. Third, the majority of LLD patients were taking antidepressant medications, which may impact imaging findings. The sample is underpowered to consider the impact of specific medications on activation. Fourth, the SLLT presented items visually, rather than orally, providing participants with an additional encoding cue, relative to verbal memory tasks that have been most widely used in the LLD literature (e.g., CVLT) where items are presented only orally. It is possible that we may have observed between-group performance differences and even greater differences in activation during encoding might have been found between the LLD and NDC groups had stimuli been presented orally, as the LLD group might have had to use more executive resources in order to effectively encode stimuli. Multimodal learning could also have assisted in encoding for the SLLT.

Conclusions

Older adults with early-onset active state MDD demonstrate a broader pattern of hypoactivation during list learning encoding relative to NDC, in regions known to be crucial to successful learning and memory. Functional differences are present despite equivalent performance on paper-and-pencil recall and recognition paradigms and may reflect different modes of processing to-be-remembered information and/or early changes predictive of incipient cognitive decline. Future studies might consider mechanisms for functional differences, including hypothalamic-pituitary-adrenal axis functioning and vascular integrity, and utilize longitudinal designs in order to understand whether functional changes are predictive of incipient cognitive decline. In order to better understand the mechanisms behind activation differences (e.g., compensation, de-differentiation) future research might also consider enrolling good and poor performers and assessing performance by activation interactions, as well as incorporating connectivity analyses to better understand the relationships among regions relevant to encoding. Given the importance of the role of the caudate in understanding manifestations of LLD (i.e., goal-directed behavior, response inhibition; Bobb *et al.*, 2012; Alexopoulos *et al.*, 2013), future research might

also consider the effects of proactive and retroactive interference on memory performance and underlying neural processes during LLD. This might entail including a retrieval phase prior to and following the distractor task, with careful effort toward minimizing movement. Finally, given the frequency of subjective memory complaints among older people with depression, it would be interesting to assess relationships between the extent of subjective memory complaints and patterns of activation during encoding of novel stimuli, as this could assist clinicians in assessing the significance of memory complaints in their patients with LLD.

Conflict of interest

None declared.

Key points

- Despite performing at similar levels on a word-list learning and memory task and having equivalent hippocampal volumes, patients with early-onset depression in late life (LLD) exhibit less activation in structures known to be relevant for new learning and memory, including hippocampus, parahippocampal gyrus, insula, and cingulate, relative to NDC.
- An important region in which the LLD group displayed greater activation than the NDC group was in left IFG, an area involved in cognitive control, language, and controlled semantic/phonological retrieval and analysis; this area may be critical for LLD patients to assist in consolidation of memory.
- Functional aberrations found in LLD patients may reflect different modes of processing to-be-remembered information, compensatory processes to assist in memory, and/or early changes predictive of incipient cognitive decline.

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