Neural Correlates Associated With Cognitive Decline in Late-Life Depression

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Objectives: *Persistent cognitive impairment (PCI) after remission of depressive symptoms is a major adverse outcome of late-life depression (LLD). The purpose of this study was to examine neural substrates associated with PCI in LLD.* **Design:** *Longitudinal study.* **Setting:** *Outpatient depression treatment study at Duke University.* **Participants:** *Twenty-three patients with LLD completed a 2-year follow-up study, and were in a remitted or partially remitted state at Year 2.* **Methods:** *At first entry to the study (Year 0), all participants had a functional magnetic resonance imaging scan while performing an emotional oddball task. For the purpose of this report, the primary functional magnetic resonance imaging outcome was brain activation during target detection, which is a measure of executive function. The Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery was used to assess cognitive status yearly, and the Montgomery-Åsberg Depression Rating Scale was used to assess severity of depression at Year 0 and every 6 months thereafter for 2 years. We investigated changes in brain activation at Year 0 associated with PCI over 2 years.* **Results:** *Patients with PCI at the 2-year follow-up date had significantly decreased activation at Year 0 in the dorsal anterior cingulate cortex, hippocampus, inferior frontal cortex, and insula compared to non-PCI patients.* **Conclusions:** *Our results suggest individuals who have LLD with PCI have decreased activation in the similar neural networks associated with the development of Alzheimer disease among nondepressed individuals. Measuring neural activity in these regions in individuals with LLD may help identify patients at-risk for cognitive impairment.* (Am J Geriatr Psychiatry 2012; 20:653–663)

Key Words: Cognitive decline, dorsal anterior cingulate cortex, hippocampus, functional magnetic resonance imaging, late-life depression

Depression in late adulthood is associated with profound changes in cognitive and emotional functioning. Cognitive impairment in some patients may persist despite remission of depressive symptoms.[1,2] Continuous impairment or further decline in cognition after remission of depression

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symptoms for is often described as persistent cognitive impairment (PCI).[3,4] Patients with PCI are of particular clinical concern because they have a higher risk of developing of dementia including Alzheimer disease (AD).[4,5] Therefore, understanding the neural mechanisms associated with PCI in late-life depression (LLD) is important for early recognition and clinical intervention among these individuals. Although PCI has been widely recognized as an adverse outcome of LLD, little is known about its neural substrates beyond findings of reduced hippocampal volume.[6]

Extensive neuroimaging studies on AD and mild cognitive impairment (MCI, prodromal AD) have been conducted in recent years,[4,7–16] and provide some information on the potential neural substrates of PCI in LLD. Structural magnetic resonance imaging (MRI) has confirmed the importance of volumetric changes in the medial temporal lobe memory system, and has specifically identified reduced volume in the entorhinal cortex as a biomarker for prodromal AD.[11] Recent functional MRI (fMRI) studies have also revealed prodromal AD affects a large-scale episodic memory network, including the anterior cingulate, insula, inferior frontal, and parietal cortices, in addition to regions typically associated with the medial temporal lobe memory system.[8,17,18]

Although there are reports showing alterations in the hippocampus, frontal and parietal cortices, and cingulate in neuroimaging studies in LLD,[19–22] little is known about which regions are specifically associated with PCI and cognitive decline. We previously studied neural substrates of depression in acute and remitted patients compared to control participants.[21] We found decreased activation in the dorsolateral prefrontal cortex, which seemed to be depressive-state related. In addition, both the acute and remitted groups showed reduced activation in the anterior-middle cingulate (BA24) and anterior portion of the posterior cortex compared with the control group during a target detection task. In that study, it was not clear whether the decreased activation in the cingulate cortex in the remitted patients was a residual effect of depression or whether it was related to possible cognitive impairment. Clarifying whether neural circuits involved in LLD with PCI are similar to those conventionally found among individuals with MCI (but never depressed) is important to better understanding the etiologies of both LLD and MCI/AD.

LLD is a heterogeneous disorder, and so are the potential causes of cognitive impairment during an acute depressive episode in LLD. There are two major types of depression-associated pathology that have been hypothesized to contribute to LLD as a risk factor for cognitive impairment. One is the progression of vascular lesions (subcortical gray matter and frontal deep white matter hyperintensities), and the other is neurotoxicity from the stress-glucocorticoid cascade. Accumulated evidence has suggested that the vascular pathology results in prefrontal-striatal dysfunction,[23–26] whereas neurotoxicity from the chronic stress-glucocorticoid cascade leads to hippocampal damage.[6,27] Butters et al.[4] have proposed pathological pathways that might link the presence of cognitive impairment in LLD to AD. Individuals in this group are presumed to have accumulated AD pathology concurrent with depression-associated pathology. Concurrence of vascular pathology in LLD with accumulated AD pathology has been postulated as the most frequently occurring pathway leading to or accelerating the development of amnestic-multidomain MCI and AD along with cerebrovascular disease.[4] Importantly, this type of cognitive impairment results in cognitive decline overtime and progression to AD. Another pathway proposed by Butters et al. is AD pathology concurrent with depression, which may reflect mood alteration due to the primary disease, and has a diagnostic endpoint of AD. Therefore, it is very likely there is AD pathology among individuals with PCI in LLD, and one can predict that PCI in LLD should have deficits in the same regions that are essential for the development of AD in nondepressed individuals, such as the hippocampus and the cingulate cortex.

In this study, we performed an fMRI scan during an emotional oddball task in LLD patients, and followed up the outcomes of cognition and depressive symptoms in the patients for 2 years. The goal of the study was to examine neural correlates of PCI occurring after a late-life episode of major depressive disorder. We hypothesized that individuals with PCI have deficits in the same brain regions (such as the hippocampus) reported in nondepressed individuals who have MCI with AD pathology.[8]

METHODS

Participants

All participants were recruited from a depression treatment study at the National Institute of Mental Health - sponsored Conte Center for the Neuroscience of Depression in Late-Life at Duke University Medical Center. In our initial fMRI study, we recruited 32 individuals who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for major depressive disorder at the time of enrollment in the treatment study. All participants were more than 60 years of age, and were either in an active depressive episode or in a remitted or a partially remitted state at the time they participated in the fMRI study. All participants completed a 2-year clinical follow-up of their depressive symptoms and cognitive status. Among them, 23 patients were in remission or in a partially remitted state at the last observation (Year 2). This study focused on the 23 patients who were in at least partial remission at Year 2.

The exclusion criteria included (1) another major psychiatric illness; (2) alcohol or drug abuse or dependence; (3) neurological illness, such as dementia, stroke, and epilepsy; (4) medical illness, medication use, or disability that would prevent the participant from completing neurocognitive testing; and (5) contraindications to MRI. Two depressed individuals meeting criteria for comorbid generalized anxiety disorder were not excluded since major depressive disorder was the primary diagnosis. A complete description of the study enrollment protocol is described elsewhere.[28] Detailed demographic and clinical assessments are listed in Table 1 for the participants who were included in our final analysis. The study was approved by the institutional review board at Duke University, and all participants provided written informed consent after the procedures had been fully explained.

Longitudinal Assessments

Depressed participants were enrolled in a longitudinal study where they received pharmacologic treatment based on a standardized algorithm.[28] Among the 23 participants, 15 were receiving monotherapy (9 on an SSRI, 2 on venlafaxine, and 4 on bupropion), 2 were receiving combination treatment (SSRI and bupropion), and 6 were receiving no antidepressants at the time of the fMRI scan. The Montgomery-Åsberg Depression Rating Scale (MADRS)[29] was used to assess symptom severity. At initial entry to the study (Year 0), the MADRS was completed by a geriatric psychiatrist, and by trained study personnel before the fMRI scan. The MADRS was administered at least once every 6 months during the 2-year study period. All raters were trained on the MADRS, and high interrater reliability (kappa > 0.9) was established.[28,30] The mean (SD) MADRS for all participants at Year 0 was 12.9 (10.5), and at Year 2 was 5.5 (5.0). In this study, we used the MADRS score to define remission. Participants with MADRS <8 for at least 6 months were considered as remitted and participants with $8 <$MADRS <15 were considered in partial remission.

Screening to rule out prevalent dementia was conducted by a geriatric psychiatrist and included a clinical evaluation, medical record review, and consultation with referring physicians when applicable. All participants also completed the Mini-Mental State Examination (MMSE). Any participants with a MMSE score below 25 were not included in this study.

Individuals participating in the study received yearly neuropsychological assessment,[28] which included the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery. The CERAD battery has demonstrated accurate case ascertainment of MCI and dementia in large scale epidemiological studies, and is effective in tracking longitudinal changes in these conditions.[31–33] We used the CERAD total score (TS) as our index of cognitive impairment. The CERAD TS is a summary of all the individual neuropsychological test scores that constitute the CERAD battery, excluding the MMSE. This metric has demonstrated high accuracy in differentiating independent samples of normal adults, MCI patients, and AD[34] patients. The CERAD TS has also demonstrated utility for tracking AD progression.[35] As described later, we used the cutoff value in the study by Chandler et al.[34] between normal cognition and MCI to define our PCI group, which includes demographic adjustment of the raw CERAD TS score for age, education, and gender. The mean (SD) of the adjusted CERAD TS across all participants was 89.8 (7.2) for Year 0 and 91.0 (9.1) for Year 2. Participants were considered as having PCI if they (1) had an adjusted CERAD TS <85 at both the Year 0 and Year 2; 2) had no improvement in CERAD TS at Year 2

TABLE 1. Clinical Profile of Participants With Persistent Cognitive Impairment Compared With Those Without Persistent Cognitive Impairment

	PCI (n = 7) Mean (SD)			Non-PCI (n = 16) Mean (SD)			PCI Versus Non-
	Year 0	Year 2	p[a]	Year 0	Year 2	p[a]	PCI at Year 0 p[b]
Age	72.1 (3.4)	–	–	66.19 (4.46)	–	–	0.006
Gender (female/male)	3/4	–	–	10/6	–	–	0.65
Education	14.7 (2.6)	–	–	16.4 (2.0)	–	–	0.1
No. subjects on antidepressants over the observation period	SSRI, 4 venlafaxine, 1 bupropion, 1		–	SSRI, 5 venlafaxine, 1 bupropion, 3 SSRI+bupropion, 2 none, 6		–	–
MADRS score	5.4 (5.7)	4.1 (4.4)	0.11	20.7 (8.9)	5.1 (3.9)	0.003	0.0001
MMSE	27.3 (1.9)	27.4 (2.4)	0.85	29.1 (1.1)	29.0 (1.4)	0.84	0.049
Adjusted CERAD Total Score	82.1 (3.4)	79.7 (4.3)	0.04	93.1 (5.7)	96.0 (5.4)	0.02	<0.0001
Memory (raw score; range = 0–50)	31.1 (3.8)	28.4 (6.7)	0.07	41.9 (4.1)	41.5 (4.7)	0.68	<0.0001
Nonmemory (raw score; range = 0–50)	39.6 (3.7)	38.9 (3.1)	0.56	42.8 (4.3)	45.4 (3.4)	0.03	0.014

Notes. [a]Paired *t*-test in comparison of Year 0 with Year 2 for the PCI group ($df = 6$) and the non-PCI group ($df = 15$) separately; [b]Comparison between the PCI group and the non-PCI group at Year 0 using two sample *t*-test for age, education, MADRS, depression episodes, MMSE, CREAD, memory and nonmemory items ($df = 21$); as well as Fisher's exact test for gender ($df = 1$).

relative to Year 0; and 3) were not in an active depressive state at Year 2. Using these criteria, 7 of the 23 participants were classified as PCI. Detailed demographic information for PCI and the non-PCI group is listed in Table 1.

Functional MRI Task

All participants completed a visual emotional oddball task at Year 0. Detailed description of stimuli and task design have been published previously.[21] In brief, there were four types of grayscale pictures presented randomly: 1) circles of varying sizes and luminance, serving as attentional targets, 2) sad distractors, 3) neutral distractors, and 4) phase-scrambled images of the distractors. The imaging session consisted of 10 runs, each containing 150 stimuli (stimulus duration = 1500 ms, interstimulus interval = 2000 ms). The participants' task was to press a response button using their right index finger upon detection of a target oddball stimulus. The attentional target, sad distractors, and neutral distractors appeared with a presentation frequency of 3.33% each, with scrambled pictures comprising the remaining 90% of stimuli. Our previous studies have consistently shown that the dorsal executive function regions are activated during target detection, whereas the emotional system is activated by sad distractors.[36] Given that we were interested in brain regions associated with PCI, we focused our analysis on brain activation during target detection as the relevant brain regions were activated under this condition in our previous studies.[21,36,37]

Image Acquisition and Analysis

Functional images were acquired on a 4.0 Tesla GE scanner (GE Signa EXCITED HD System; GE Healthcare, Milwaukee, WI) with identical acquisition parameters as Wang et al.[36] Oblique spoiled gradient-recalled acquisition images (three-dimensional, whole-brain) were acquired parallel to the anterior commissure–posterior commissure plane thickness of 1.9 mm. Inward spiral gradient images were acquired with the following parameters: TR (Repetition Time) = 2000 ms, TE (Echo Time) = 31 ms, FOV (Field of View) = 24 cm, flip angle = 90°, matrix = 64 × 64 × 34, slice thickness = 3.75 mm with 3.75 mm^3 isotropic voxels. FEAT (FMRI Expert Analysis Tool) Version 5.98, part of the FSL analysis package (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl), was used to conduct image pre-processing procedures. These procedures include slice-timing alignment, motion correction, coregistration, non–brain voxel extraction, normalization, smoothing (5 mm^3 kernel) and high–pass temporal filtering (1/60 Hz).

The general linear model was used for the first-level FSL FEAT analysis, and contained three types of

events: negative distractors, neutral distractors, and targets. However, we only focused on activation to target events in the analysis at the group level. Results for targets were combined across runs for each participant, using fixed-effects models. At the group analysis level, we used a mixed effects analysis for controlling within- and between-subjects variation. Given that only 7 of 23 participants had PCI more than the 2-year period, we used the "outlier deweighting function" (a mathematic tool in the FSL FEAT software) to ensure the findings were not biased by outliers. The outlier deweighting method models errors as being both from normal population and from the outliers. Furthermore, it uses variance information from lower levels in the hierarchy.[38] Statistical results were thresholded at a voxel significance level of $Z > 2.3$ and a whole-brain-corrected cluster significance threshold of $p < 0.05$. First, we used voxel-wise analysis of variance (ANOVA) to compare the activation difference in response to targets between participants with PCI and participants without PCI. Then we conducted a regression analysis to examine brain regions that were linearly associated with cognitive performance at Year 0 and with cognitive decline more than the 2 years by using the CERAD TS at Year 0 and the change in CERAD TS (Year 2–Year 0) as independent regressors (i.e., orthogonalized to each other). We controlled for the potential confounding effects of age, education, and severity of depression in all of these analyses.

Finally, we conducted a conjunction analysis to obtain regions that 1) indicated significant differences between PCI and with non-PCI individuals and 2) were correlated with cognitive decline. Only the regions that overlapped in the conjunction analysis were considered important for predicting subsequent PCI. To illustrate the correlation, we conducted ROI (region of interest) analyses to produce regression plots by extracting the significant clusters that differed between PCI and non-PCI groups. Confirmatory regression analyses were conducted to correlate mean peak signal changes in each ROI with unadjusted CERAD TS at Year 0 and the change in unadjusted CERAD TS (Year 2 – Year 0) using a statistical threshold of $r > 0.4$ and $p < 0.05$ (two-tailed). The ROI analysis was used to confirm that the results of the voxel-wise correlation analyses were not driven by outliers.

RESULTS

Comparison of the Clinical Profile Between the PCI and Non-PCI Groups

Seven of 23 participants had PCI, which resulted in a 30% prevalence among our sample of older adults with LLD. A detailed comparison of the clinical profile between the two groups is presented in Table 1. The PCI group was significantly older than the non-PCI group (two sample *t*-test, $t_{[21]} = 2.16$, $p < 0.02$), and was less depressed than the non-PCI group at the time they participated in the fMRI scan at Year 0 (two-sample *t*-test on MADRS score, $t_{[21]} = 4.68$, $p = 0.001$). Only 1 of the 7 patients with PCI (14%) was in an active depressive state at Year 0, whereas the number of non-PCI individuals with active depression was 11 of 16 (69%). Given the difference in age and severity of depression (at Year 0) between the PCI and non-PCI groups, we controlled for age, education, and MADRS in our whole-brain voxel-wise fMRI analyses.

Cognitive performance on the CERAD TS was significantly different between the two groups at both Year 0 and Year 2. While the PCI group had significantly lower cognitive performance from Year 0 to Year 2 (paired *t*-test on adjusted CERAD TS score, $t_{[6]} = 2.20$, $p = 0.04$), the non-CI group had significantly higher cognitive performance (paired *t*-test, $t_{[15]} = 2.78$, $p = 0.02$) over the 2-year period. Since the majority of the participants in the non-PCI group were acutely depressed at baseline, improved CERAD TS scores at Year 2 for this group may suggest a mood-congruent improvement in cognition.

Subdividing the CERAD TS into memory and nonmemory items revealed that the PCI group had lower scores than the non-PCI group at both Year 0 and Year 2 across both groups of items, indicating that the lower CERAD TS of PCI participants included both memory and nonmemory domains (Table 1).

Activation Associated With PCI

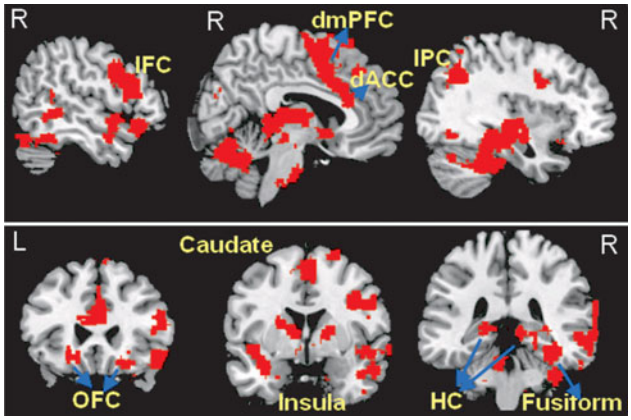
Our previous research showed that target stimuli in the oddball task activated the dorsal executive system, including the dorsolateral prefrontal cortex, dorsal anterior cingulate (dACC), anterior portion of the posterior cingulate, inferior parietal cortex,

insula, striatum, and cerebellum.[21,36,37] Here, we found that individuals with PCI over the 2 years had significantly decreased activation in both dorsal anterior cingulate (dACC, BA24) and posterior cingulate cortices at Year 0 compared with non-PCI patients. The activation in the dACC was extended to the dorsal supplementary motor cortex (or so-called dorsomedial prefrontal cortex, BA6). We refer this region as dACC/dmPFC later on in the text. Decreased activations in PCI relative to non-PCI group were also found in bilateral hippocamal formation (entorhinal cortex), right inferior frontal cortex, left inferior parietal cortex, left insula, left thalamus, right caudate, and bilateral cerebellum (Figure 1, Table 2). To confirm the results from the voxel-based analysis, ROI analysis on the significant clusters including the dACC/dmPFC and right hippocampus were conducted. Significant differences between the PCI and non-PCI groups in these ROIs were tested using a two-sample Kruskal-Wallis test. The results confirmed the significant difference between the PCI and non-PCI groups (dACC/dmPFC, $\chi^2_{[1, n = 23]} = 5.47$, $p = 0.02$; hippocampus, $\chi^2_{[1, n = 23]} = 10.72$, $p = 0.001$).

Because six participants in the non-PCI group were not taking antidepressant medication, we examined whether medication status influenced our results. By removing these 6 participants from the non-PCI group, the comparison groups consisted of 7 PCI and 10 non-PCI participants. Removing these individuals did not change the results significantly.

Furthermore, regression analysis across the 23 participants (controlling for age, education, and MADRS) revealed that activation in many regions at Year 0 was correlated with the degree of subsequent cognitive decline (Year 2 CERAD TS – Year 0 CERAD TS). These regions included the dACC (BA24, extended to middle cingulate), anterior portion of the posterior cortex (BA31), bilateral hippocampus, bilateral middle temporal cortex, bilateral orbitofrontal cortex, bilateral insula, and left inferior parietal cortex. (Figure 2, Table 3). As shown in Figure 3 from the conjunction analysis, right dACC, hippocampus, bilateral insula, right inferior frontal cortex, and fusiform cortex were the regions that overlapped across the two analyses, indicating that activation in these regions at Year 0 was associated with persistent cognitive impairment.

FIGURE 1. Brain regions showing significantly reduced activation in the PCI group compared with the non-PCI group.



dACC: dorsal anterior cingulate; dmPFC: dorsomedial prefrontal cortex; HC: hippocampal complex; IFC: inferior frontal cortex; IPC: inferior parietal cortex, OFC: orbitofrontal cortex.

Activation Associated With Cognitive Function at Year 0

We found that the activation in the dACC/dmPFC (BA24 and BA6) and the left inferior parietal cortex cortices were significantly correlated with the CERAD TS at Year 0 (Figure 4, Table 4). Although the ROI plot in Figure 3 also showed a correlation between hippocampus activation and TS at Year 0 (Figure 3, lower left), it did not pass the threshold in the whole brain analysis.

Activation Associated With Both Cognitive Function at Year 0 and PCI

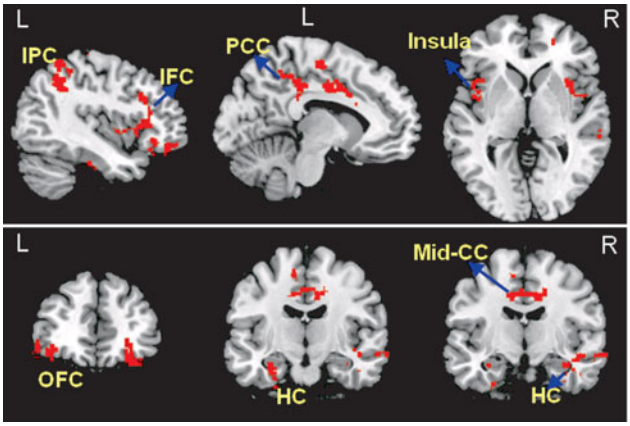
Since the majority of our patients had depressive symptoms in varying degrees at the time of their fMRI scan, it is very likely that cognitive performance in some participants at Year 0 was related to depression status and depression severity. In addition to using MADRS as a covariate to control the influence of depression severity (note that the MADRS was not correlated with CEREAD TS at baseline, $r_{[22]} = 0.38$, $p = 0.08$), we also did a conjunction analysis to identify the overlapping regions where activation was associated with 1) cognitive function at Year 0, 2) PCI status, and 3) cognitive decline over the 2 years. We found that the dACC (BA24, the voxels in white color in Figure 4) showed an overlap in the

TABLE 2. Brain Regions Showing Significantly Decreased Activation During Targets Detection at Year 0 in Participants With Persistent Cognitive Impairment Compared to Participants Without Persistent Cognitive Impairment

Regions	Brodman Area	Voxel Size	*Z* Max	Peak Voxel (MNI Coordinates)		
				X	*Y*	*Z*
Right parahippocampus		21043	4.69	38	34	-14
Right entorhinal cortex			3.2	23	9	-27
Right superior temporal cortex	BA21		3.11	44	-7	-14
Right supplementary motor cortex	BA6	2398	3.86	18	20	66
Dorsal anterior cingulate	BA24		3.12	1	11	37
Right inferior frontal cortex	BA44	1102	3.13	52	8	32
Left superior parietal cortex	BA7	930	3.15	−26	−64	46
Left inferior parietal cortex	BA40		2.83	−34	−46	46
Left entorhinal cortex			3.0	−23	2	−28
Left temporal pole	BA38		4.33	−32	4	−20
Left thalamus			3.32	−14	−13	16
Left insula	BA13		3.11	−41	−4	−7
Cerebellum			4.25	−42	−74	−22
Right caudate		229	3.51	9	18	7

MNI: Montreal Institute of Neurology.

FIGURE 2. Brain regions revealing a linear correlation between brain activation to targets at Year 0 and cognitive decline measured by the change in CERAD TS (Year 2 – Year 0).



dACC: dorsal anterior cingulate cortex, HC: hippocampal complex, IFC: inferior frontal cortex, IPC: inferior parietal cortex, PCC: posterior cingulate cortex, OFC: orbitofrontal cortex.

conjunction analysis, whereas activation in the left inferior parietal cortex (Figure 4) was only associated with cognitive function at Year 0, and did not overlap with the PCI-related region.

DISCUSSION

The purpose of the study was to investigate neural substrates in depressed patients that can predict PCI. We found reduced activation in the dACC, hippocampus, inferior frontal cortex, and insula in PCI patients compared with non-PCI patients. In particular, low activation in the dACC, hippocampus, insula, and fusiform cortex were also associated with greater cognitive decline over the 2-year period. Therefore, reduced activation in these regions in patients with LLD suggests an increased likelihood of PCI over a 2-year period.

Decreased activation in the medial temporal lobe (hippocampus and fusiform gyrus) and cingulate cortex has been frequently found in patients with MCI and AD.[15, 39] Consistent with our prediction, depressed patients with PCI indeed had deficits in the same neural circuits as nondepressed patients with MCI. Although the results do not directly imply that PCI in LLD necessarily share the same neuropathology as MCI/AD without depression, the results suggest that PCI in LLD both demonstrate alterations in the same neural circuits, which explains commonalities in cognitive deficits. A large sample size and a direct comparison between PCI in depression and never-depressed MCI are needed to further confirm the results. Confirming these results is important since it will not only allow us to predict cognitive impairment in patients with LLD, but it will also deepen our understanding of neural mechanisms linking depression with MCI

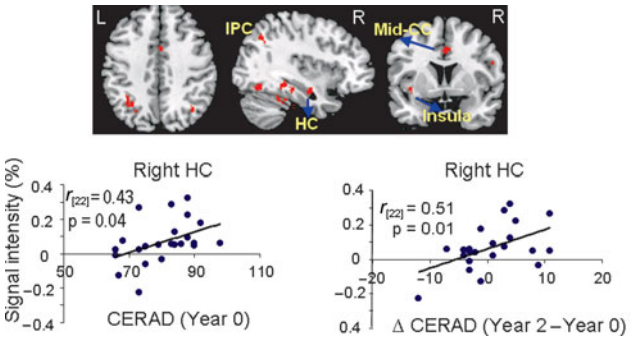
Another core finding of the study is that decreased activation of the dACC/dmPFC was not only correlated with cognitive function at Year 0, but also

TABLE 3. Brain Regions Showing Linear Correlation of Activation During Targets Detection With the Degree of Cognitive Decline Measured by the Change of CERAD Total Score (Year 2 – Year 0)

Regions	Brodman Area	Voxel Size	*Z* Max	Peak Voxel (MNI Coordinates)		
				X	*Y*	*Z*
dmPFC/Cingulate Cortex		1504				
Right dorsal anterior cingulate	BA24		7.57	10	4	38
Left posterior cingulate cortex	BA31		6.71	−4	−14	46
Left posterior cingulate cortex	BA31		6.67	−10	−30	40
Left inferior parietal cortex	BA40	985	6.96	−30	−58	46
Right middle temporal cortex	BA22	569	6.32	60	−36	−4
Right hippocampus			5.33	36	−10	−22
Left parahippocampus	BA35	294	5.44	−26	−14	−32
Left hippocampus			4.16	−29	−11	−20
Cerebellum			5.05	−24	−30	−28
Left superior temporal cortex	BA22	355	6.03	−42	−28	4
Left inferior temporal cortex	BA37	280	4.86	−42	−42	−14
Left orbital frontal cortex	BA11	556	6.01	−42	42	−14
Right orbital frontal cortex	BA11	329	4.56	28	46	−16
Left inferior frontal cortex	BA45	614	6.04	−42	28	4
Left insula	BA13		3.80	−42	16	2
Right insula	BA13	261	5.84	38	12	−4

MNI: Montreal Institute of Neurology.

FIGURE 3. The brain maps illustrating the overlapped brain regions showing significantly reduced activation in the PCI group compared with the non-PCI group and meanwhile the activations significantly correlated with the degree of cognitive decline based on the conjunction analysis.



The plots illustrating the relationship of brain activation in the hippocampus with cognitive function at Year 0 (left) and with the degree of cognitive decline over the 2 years (right). Mid-CC: middle cingulate cortex, HC: hippocampal complex, IPC: inferior parietal cortex.

associated with PCI. Involvement of ACC in the pathology of LLD has been well documented in the literature,[21,22,40,41] although the reported change in directionality was different depending on the type of task employed in different studies. We have previously shown reduced activation in the ACC regardless of depression state.[21] Our current results further suggest that deficits in dACC function could be a leading cause of cognitive impairment and cognitive decline in LLD. Our results are consistent with positron emission tomography imaging studies that have shown beta-amyloid deposition in both geriatric depressed patients and MCI patients in many of these anterior and posterior cortical regions.[42,43] Therefore, decreased activation to targets in this region warrants closer clinical follow-up. Decreased activation in the left inferior parietal cortex was only associated with cognitive function at Year 0 but not with PCI, which suggests that the decreased activation in the left inferior parietal cortex can be normalized after remission of depression.

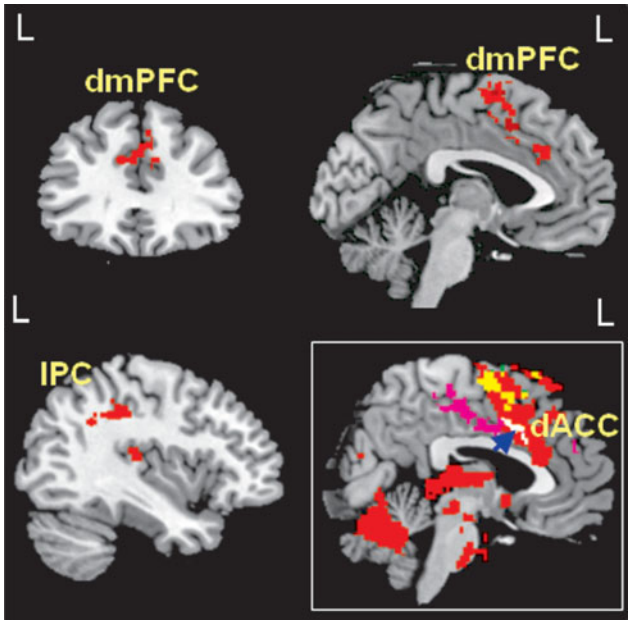
Activation in the hippocampus was associated with cognitive decline and correlated with cognitive function at Year 0 in the ROI analysis but not in the whole-brain corrected analysis, suggesting that individual variance plays an important role. In our sample, individuals who were in remission had lower cognitive function, reduced activation in the hippocampus, and greater cognitive decline 2 years later. Therefore, our results were not confounded by depressive symptoms. Hippocampal atrophy and reduced hippocampal activation are hallmarks of AD. Reduced hippocampal volume is also the most

TABLE 4. Brain Regions Showing Significant Correlation of Activation During Targets Detection With the CERAD Total Score at Year 0

Regions	Brodman Area	Voxel Size	*Z* Max	Peak Voxel (MNI Coordinates)		
				X	*Y*	*Z*
Left inferior parietal cortex	BA40	728	5.81	−56	−32	42
Inferior parietal cortex	BA40		4.60	−60	−38	40
Left supplementary motor cortex	BA6	689	5.58	−6	0	60
Dorsal anterior cingulate	BA32		4.84	−2	30	30

MNI: Montreal Institute of Neurology.

FIGURE 4. Brain regions revealing a linear correlation between brain activation to targets with cognitive function as measured by CERAD TS at Year 0.



The image inside the white box (lower right) illustrates the overlapping voxels from three analyses: 1) activations that were correlated with cognitive function at Year 0 (green), 2) activations that were correlated with cognitive decline over the 2 years (purple), and 3) the regions which significantly distinguished the PCI and non-PCI groups (red). The overlapping voxels among the three analyses are in white, where the arrowhead is pointed. The overlapping voxels between analyses 1) and 3) are indicated in yellow. dACC: dorsal anterior cingulate, dmPFC: dorsomedial prefrontal cortex, IPC: inferior parietal cortex.

consistent finding in studies on cognitive impairments in patients with LLD.[6,44,45] Here, we extended previous findings and showed that low activation in the hippocampus in remitted depression could predict cognitive decline.

Thirty percent of patients with LLD in our sample had PCI, which is consistent with previous findings.[1] One limitation of this study is the small sample size. Another limitation of the study is that for those remitted patients who had PCI, they also had cognitive impairment at Year 0. As a result, we cannot determine whether the cognitive impairment appeared before or after depression and whether it was independent of depression. Further follow-up study on remitted patients without cognitive impairment would be necessary to clarify the causal relationship of cognitive impairment and depression.

In summary, our study showed that PCI in LLD shares deficits in a large-scale brain network similar to MCI/AD. Reduced activation in the dACC was associated with cognitive performance at Year 0 and cognitive decline over the 2-year period. Therefore, reduced activation in the dACC could be an indicator of acute cognitive dysfunction, longitudinal cognitive dysfunction, or both. Reduced activation in the hippocampus seemed to be a clearer indicator of PCI. Future studies with larger sample sizes, direct comparison of PCI and never-depressed MCI, and better tracking of the onset of cognitive impairment are important for further improving our understanding of the pathophysiology underlying PCI in depression, and the relationship between the circuitry in MCI and PCI with depression. An understanding of the neural circuitry of PCI in depression would inform the design of future mechanistic studies to understand the role of neurodegenerative (atrophy, beta-amyloid) and cerebrovascular processes relative to the functional neuroanatomic abnormalities.

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