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Imaging Alzheimer Pathology in Late-Life Depression With PET and Pittsburgh Compound-B

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Abstract

There is increasing evidence for an empiric link between late-life depression and Alzheimer disease (AD). The neuropathology of AD, previously only confirmed at autopsy, may now be detectable in vivo using selective imaging ligands for β -amyloid. Positron emission tomography (PET) with [¹¹C] 6-OH-BTA-1 [Pittsburgh Compound-B (PiB)] has shown high tracer retention in cortical areas in patients with clinical diagnoses of probable AD and low retention in age-matched controls. We also previously reported variable PiB retention in patients with mild cognitive impairment (MCI). In this study, we used PiB-PET to evaluate whether amyloid is present in elders with treated major depression, many of whom have persistent cognitive impairment. We evaluated 9 subjects with remitted major depression [3M: 6F, mean (SD) age=71.8(5.7) y]. Seven of the 9 depressed subjects also met criteria for the diagnosis of MCI. PiB-PET data from healthy elders [n=8; mean (SD) age=71.5(3.0) y] were used for comparison. PET was acquired with arterial sampling and PiB retention was quantified using magnetic resonance imaging-guided cortical regions and graphical analysis of time-activity data; arterial line failure led to exclusion of 1 depressed subject. The data demonstrated variably elevated PiB retention. PiB retention in the 2 depressed subjects with normal cognitive ability was in the range of nondepressed cognitively normal subjects. PiB retention in 3 of the 6 depressed subjects with MCI fell in the range of subjects with AD. PiB retention in the remaining

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3 depressed subjects with cooccurring MCI was variable and generally was intermediate to the other subjects. Our findings are consistent with and supportive of the hypothesis that depression may herald the development of AD in some individuals.

Keywords

depression; Alzheimer disease; amyloid; brain; emission tomography

There is clear and increasing evidence of an association between late-life depression and Alzheimer disease (AD). Reported rates of dementia among late-life depression patients vary considerably, from 10% to nearly 90%.^{1–3} A meta-analysis of the results from 7 case-control and 6 prospective studies suggests that depression in late life approximately doubles an individual's dementia risk.⁴ A more recent meta-analysis performed by Ownby and colleagues⁵ came to the same conclusion, that is, that a history of depression at any point in life approximately doubles one's risk of developing AD. Data from the multi-institutional research in Alzheimer's Genetic Epidemiology (MIRAGE) study suggest that depression occurring up to 25 years before the onset of AD may still serve as a predisposing factor for dementia.⁶ Conversely, AD patients also have a high prevalence of coexisting depression, ranging from 10% to 50% and occurring in both mild and later stages of dementia.^{7–10} The frequency with which depression and dementia coexist in the elderly supports a shared mechanistic and/or etiologic foundation between the 2 conditions.

Indeed, depression may be the initial sign of neurodegenerative disease, and alone may be regarded as a risk factor for the later development of dementia. The presence of cognitive impairment may further increase the risk of developing AD among depressed elders. The risk of dementia is increased nearly 5-fold in depressed elders with reversible cognitive dysfunction over that observed in patients with depression without cognitive impairment.¹¹ Further, 20% of individuals in the Cardiovascular Health Study who had mild cognitive impairment (MCI) and 32% of those with dementia also exhibited depressive symptoms.¹² The risk of dementia in patients with MCI also seems to be greater in those individuals who also exhibit neuropsychiatric symptoms, particularly depression.¹²

Petersen and colleagues¹³ initially described a form of MCI in which there is a singular, substantial deficit in episodic memory, accompanied by otherwise normal levels of function in other cognitive domains and no measurable functional impairment in daily life. There is broad agreement that most individuals with amnesic MCI have subclinical AD, and most longitudinal studies have been limited to this subtype.^{13–16} Evolution of the MCI concept recognizes heterogeneity among individuals.¹⁷ Lopez and colleagues¹⁸ have defined a multiple cognitive domain (MCI-MCD) subtype, in which subjects experience either a singular deficit in a nonmemory domain (eg, in visuospatial, executive, memory, etc.) or very mild impairment in MCDs (which may or may not include memory). In studies by Butters et al¹⁹ and Bhalla et al,²⁰ approximately one half of elderly depression patients (regardless of whether they were depressed or in remission) met cognitive criteria for MCI, with most of them exhibiting the MCI-MCD subtype. The National Alzheimer's Coordinating Center Uniform Data Set very recently implemented a new diagnostic system for use by Alzheimer Disease Research Centers, which contains 4 MCI subtypes that maximize the distinction between those who do and those who do not, have a deficit in episodic memory: (1) amnesic MCI—memory impairment only, (2) amnesic MCI—impairment in memory plus 1 or more other domains, (3) nonamnesic MCI—impairment in a single nonmemory domain, and (4) nonamnesic MCI—impairment in multiple nonmemory domains. As most longitudinal studies have employed the original Petersen criteria of MCI, the prognostic significance of amnesic MCI accompanied by impairment in additional domains and nonamnesic MCI is less clear.

Brain β -amyloid accumulation, believed to be due to an imbalance between its production and clearance, is a key pathologic underpinning of AD.²¹ Although the bulk of our knowledge of the pathophysiology of neurodegenerative disorders is based on postmortem studies, which are biased toward end-stage disease, there is evidence to suggest that amyloid deposition may occur as early as a decade before clinical symptoms.²² This evidence is further supported by studies that show that subjects who die at the stage of MCI have sufficient plaques and tangles to meet criteria for AD.^{23,24} The recent development of high-affinity positron emission tomography (PET) imaging ligands for amyloid now permits the evaluation of the neuropathologic link among depression, cognitive impairment, and AD in vivo.^{25,26} In initial human studies with Pittsburgh Compound-B (PiB)-PET imaging, we demonstrated variable accumulation of β -amyloid in the brains of nondepressed individuals with MCI.^{27–29} Several very recent studies suggest that 52% to 62% of individuals with MCI are PiB-positive, or exhibit PiB retention well above the mean of cognitively normal individuals and in the range of individuals with AD.^{30–32} The current study will extend these findings to perform the first in vivo human investigation of whether amyloid neuropathology is present in elders with major depression.

METHODS AND MATERIALS

Subject Selection

We studied a total of 9 subjects over age 65 with treated late-life major depression [3 men, 6 women; mean (SD) age=71.8 (5.7) y] (Table 1). All of these subjects presented to a late-life depression clinic and remitted with escitalopram as part of an ongoing clinical trial of maintenance therapy in geriatric depression. After successful antidepressant therapy, subjects underwent detailed neuropsychiatric evaluation for dementia and MCI that included neuropsychologic assessment and other clinical measures.

Subject evaluation included a psychiatric interview using the structured clinical interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).³³ The Mini-Mental State Examination (MMSE)³⁴ was administered to evaluate general cognitive status. Before antidepressant treatment, subjects underwent thorough psychiatric evaluation at our late-life depression clinic and met DSM-IV criteria for current major depressive episode (nonpsychotic),³⁵ and consensus expert evaluation confirmed the diagnosis of depression [mean (SD) Hamilton Depression Rating Scale Scores: pretreatment: 18.2 (2.5); posttreatment: 7.1 (1.5)]. Individuals with unstable medical illness, substance abuse over the past year, history of neurologic disorder or significant head trauma (defined as loss of consciousness for >30 min), and/or active malignancy were not studied.

To aid in diagnostic adjudication of cognitive status, a comprehensive neuropsychologic assessment^{36–49} was performed by 2 examiners who were highly trained and closely supervised by a senior neuropsychologist with expertise in geriatric neuropsychiatric disorders (M.A.B.). In all the cases, subjects were tested within a few weeks after responding to antidepressant treatment. The neuropsychologic test results along with the other relevant data [eg, results from psychiatric and neurologic evaluations, magnetic resonance (MR) imaging, activities of daily living evaluation, etc] were forwarded to the University of Pittsburgh Alzheimer Disease Research Center (ADRC), where they were used for diagnostic adjudication.

PiB-PET data from healthy elders [n=8; 2 men, 6 women; mean (SD) age 71.5 (3.0) y] were used for comparison. Data from 6 of these nondepressed controls were previously included in other published data.^{27–29} For these healthy control subjects, additional exclusion criteria included a history of neurologic or psychiatric disease and/or a first-degree relative with a psychiatric or neurodegenerative disorder.

All subjects provided written informed consent before study entry, as approved by the University of Pittsburgh Institutional Review Board and Radioactive Drug Research Committee.

Imaging Acquisition

The radiosynthesis of PiB was performed as initially detailed by Mathis and colleagues⁵⁰ and using a simplified synthesis described by Price et al.²⁷

PET scans were acquired using an emission computerized axial tomography high resolution+ (ECAT HR+) PET scanner (Siemens Medical Solutions, Erlangen, Germany) in 3-dimensional⁵¹ mode [63 transaxial planes, 2.4-mm thickness; in-plane resolution=4.1 mm full-width at half-maximum over a 15.2-cm field-of-view]. Subjects were positioned parallel to the canthomeatal line and the entire brain was included in the scan. After a 10-minute transmission scan acquired using rotating rods of 68Ge/68Ga, emission imaging immediately followed intravenous injection of 14.8 ± 1.6 mCi high-specific activity (approximately 1000 mCi/ μ mol) PiB. PET scanning was performed for 90 min (except in 1 subject who was only able to cooperate for the acquisition of a total of 70 min of emission data). A Neuro-insert (CTI PET Systems, Knoxville, TN) placed in the camera gantry was used to reduce random coincidences.⁵¹ Head movements were minimized by the use of a thermoplastic mask and headholder system. PET data were also corrected for radioactive decay and scatter using a model-based approach.⁵² PET image reconstruction was performed using filtered back-projection (Fourier rebinning, 2D backprojection, Hann filter: kernel full-width at half-maximum= 3 mm) for a final reconstructed image resolution of about 6 mm (transverse and axial, in-house measurements, data not shown).

Dynamic arterial blood sampling was performed during emission scanning. In 1 depressed subject, arterial line failure caused loss of PET data. Plasma data were corrected for the presence of radiolabeled metabolites as determined by high-performance liquid chromatography or extraction analyses as detailed by Price et al.²⁷ and Lopresti et al.²⁸

MR imaging was successfully performed in all subjects for the dual purpose of guiding region-of-interest (ROI) placement and performing partial volume correction. MR images were acquired using a Signa 1.5 Tesla scanner (GE Medical Systems, Milwaukee, WI) with a standard head coil. PET analysis focused on T1-weighted volumetric spoiled gradient-recalled (SPGR) MR images. The SPGR sequence (echo time=5, repetition time=25, flip angle=40 degrees, number of excitations=1; section thickness=1.5 mm with no intersection gap) was acquired in the coronal plane. PET-MR registration was accomplished using automated image registration.⁵³ Pixels corresponding to scalp and calvarium were removed from the SPGR MR images⁵⁴ to facilitate registration with the PET images. Standard clinical T2-weighted and fluid-attenuated inversion recovery (FLAIR) axial images were also acquired to exclude unexpected pathology.

Image Analysis

ROIs were hand-drawn on the coregistered MR images according to anatomic landmarks using guidelines established within the laboratory and transferred to the dynamic PET data for regional sampling. We have previously assessed and reported high interrater reliability (intraclass correlation coefficient ≥ 0.90) for measurements of ROIs (eg, 27). Coauthor Jessica A. Hoge was the sole rater for this study and we did not assess her intrarater reliability. ROIs were sampled on multiple consecutive MR images on which the structure was visualized and right and left regions were combined to reduce noise. Regions sampled included posterior cingulate, parietal cortex, frontal cortex, sensory motor cortex, occipital cortex, subcortical

white matter, pons, mesial temporal cortex (including amygdala, hippocampus, and a portion of the parahippocampal gyrus), and cerebellum.

Time-activity data (0 to 90 min postinjection) were generated from the dynamic image data for each ROI. Data were analyzed using a Logan graphical^{55,56} (35 to 90 min postinjection interval) approach. Regional PiB distribution volume (DV) values were normalized to the PiB reference (cerebellum) to yield DV ratios (DVRs). The DVR was chosen, rather than the binding potential (BP),⁵⁷ as the primary outcome measure [$DVR=BP+1$]. For the controls with null levels of PiB retention, the average regional PiB BP value varied about 0, yielding both positive and negative BP values. On the basis of earlier work comparing compartmental and other approaches, the DVR has been shown to provide a robust and physiologically tenable non-negative outcome measure across control, MCI, and AD subjects.^{27,28} The DVR measure can be directly related to the free binding site pool (Bmax) and the ligand dissociation constant (K_D).

Regional DVR values were corrected for partial volume effects because of differential cerebral volume loss among the elderly subjects. For this purpose, we applied a previously validated 2-component MR-based atrophy correction algorithm,⁵⁸ as modified and routinely used in our laboratory.⁵⁹

Data analyses were performed using the Statistical Package for the Social Sciences version 14.0.⁶⁰ The Wilcoxon rank-sum test was applied to assess differences in age, educational level, and cognitive function between patients and healthy control subjects. A 2-way repeated measures analysis of variance was used to determine whether the fraction of metabolites in plasma at 2, 10, 30, 60, 75, and 90 minutes postinjection differed between patients and control subjects. For all analyses, statistical significance was set at the $P<0.05$ level.

RESULTS

There were no significant differences in age ($P = 0.64$) or education ($P = 0.08$) between the patients and healthy control subject groups (Table 1). Although the MMSE scores tended to be higher in controls [mean (SD)=29.1 (1.1)] than patients [mean (SD) 28.2 (1.8)], this difference was not significant ($P = 0.33$).

Subjects' scores on the neuropsychologic test battery are presented in Table 2. Performance is expressed in Z-scores based on the mean and standard deviation of nondepressed control subjects recruited into our late-life mood disorders research center. The characteristics and test performance of these control subjects have been published previously.^{19,20} Cognitive status of depressed patients (including MCI subtype, if applicable) and impaired domains (if applicable) are listed in Table 3 for each subject. Of the 9 depressed subjects whose depression remitted with escitalopram, detailed neuropsychologic evaluation showed that 2 had no cognitive abnormalities and 7 qualified for a diagnosis of MCI. Of the 7 with MCI, 3 met criteria for amnesic MCI—memory impairment plus 1 or more other domains, 2 met criteria for nonamnesic MCI—single domain, and 2 met criteria for nonamnesic MCI—multiple domains (PET data not available in 1 of these latter subjects because of arterial line failure) (Table 3). In summation, of all 9 depressed MCI subjects evaluated, 7 had MCI; 3 had amnesic MCI and 4 had nonamnesic MCI.

In a comparative analysis of 5 subjects with 90-minute emission data analyzed using the Logan graphical method with the 35 to 70 minutes postinjection interval and the 35 to 90-minutes postinjection interval, there was no systematic difference (ie, directional bias) in regional DVR values and variability was small (within 6%). Therefore, we elected to include the 1 subject with 70 minutes of emission data in the final analysis.

There was no significant difference between controls and depressed subjects in PiB retention in the cerebellar reference region [mean (SD)=3.78 (0.64)] and control [mean (SD)=3.88(0.68)] groups ($P=0.64$). Among control subjects, regional PiB DVR values in areas where amyloid accumulation is expected in AD (eg, posterior cingulate/precuneus, parietal cortex, frontal cortex) were within the range previously published for healthy subjects. These subjects' values were also similar for those regions with little or no amyloid accumulation in AD (sensory motor cortex, subcortical white matter, pons).

Figure 1 shows representative PET images in depressed subjects with a range of cortical PiB accumulation including "control-like" in 2 subjects, mild-to-moderate uptake in 2 subjects, and extensive "AD-like" uptake in 1 subject. Regional DVR values for the depressed group spanned from similar to the control group to within the range observed in subjects with probable AD (Fig. 2).²⁸ Interestingly, in the areas where amyloid deposition is typically prominent in AD, 2 of the 3 depressed subjects with amnesic MCI and 1 of the 3 with nonamnesic MCI had PiB retention in the AD range. In contrast, PiB retention in the 2 cognitively normal depressed subjects fell in the range of control subjects. Therefore, 3 of 6 depressed subjects with MCI who were successfully scanned showed PiB retention that was clearly above control levels in at least 1 cortical area, indicating the presence of amyloid accumulation. In the frontal cortex, 2 depressed subjects without cognitive impairment showed PiB retention similar to control values (Fig. 3). Although not statistically significant possibly because of small sample sizes, frontal PiB DVR values were higher among amnesic ($n=3$) versus nonamnesic MCI ($n=3$) subjects.

No effect of subject group was observed in the rate of metabolism of PiB in plasma ($P=0.82$). At 6 postinjection intervals, similar mean fractions of the parent compound (2 min: $82.7\% \pm 10.6\%$ SD, $83.9\% \pm 5.2\%$ SD; 10 min: $31.3\% \pm 10.0\%$ SD, $32.8\% \pm 8.2\%$ SD; 30 min: $10.3\% \pm 4.2\%$ SD, $32.8\% \pm 2.4\%$ SD; 60 min: $7.7\% \pm 2.0\%$ SD, $7.3\% \pm 2.1\%$ SD; 75 min: $7.1\% \pm 2.4\%$ SD, $6.6\% \pm 1.6\%$ SD; 90 min: $6.7\% \pm 1.4\%$ SD, $5.6\% \pm 2.1\%$ SD) were measured in plasma in the depressed and control subjects, respectively.

DISCUSSION

This initial imaging study of AD neuropathology in elders with major depression supports growing clinical and epidemiologic data that late-life depression may be either a substantial risk factor or in some cases a potential early manifestation of AD. Among 9 nondemented subjects with treated depression and variable cognitive impairment (7 with MCI), approximately one-half demonstrated PiB retention indicative of brain β -amyloid accumulation in cortical areas in a pattern characteristic of early AD (3 of 8 with arterial lines were definitely PiB-positive, 1 of the remaining 5 had intermediate levels of PiB). Thal and colleagues⁶¹ described 5 distinct, sequential phases of brain amyloid deposition, where phase I demonstrates exclusively neocortical involvement (frontal, parietal, temporal, occipital) and later phases progressively show β -amyloid deposits in the entorhinal region and insula, thalamus, putamen, caudate nucleus, cholinergic nuclei of the basal forebrain, and brainstem nuclei. The latest phases indicate β -amyloid in the cerebellum and additional brainstem nuclei. Although both β -amyloid deposition and altered tau metabolism leading to neurofibrillary tangle formation are hallmarks of AD, it is pathologically defined by the presence of β -amyloid-containing neuritic plaques.⁶² The bulk of our knowledge of the pathophysiology of neurodegenerative disorders is based on postmortem studies, which are biased toward end-stage disease. However, a postmortem study in Down syndrome, in which early AD is common, supports the hypothesis that β -amyloid deposition may occur as early as a decade before clinical symptoms.²² In vivo data with PiB-PET imaging further support the accumulation of β -amyloid in the brains of individuals with only mild cognitive dysfunction.^{30–32} Demonstration of this new capability to detect the presence of AD pathologic changes in vivo has important

implications for patient prognosis and differential management of individuals with late-life depression.

The clinical relevance of identifying those individuals at greatest risk of developing AD is growing as new therapeutic approaches directed at modifying AD progression evolve. Among subjects with MCI in memory disorders clinics, the overall rate of progression to dementia seems to be approximately 15% per year across several studies.^{13–16} The Alzheimer's Disease Cooperative Study Group reported an annual rate of progression to AD of 16% among 769 MCI subjects followed over 3 years.⁶³ Approximately 50% of individuals with MCI progress to develop AD over a 5-year period, indicating that a diagnosis of MCI alone is not a sufficient predictor of dementia prognosis.^{14,16,64,65} On the basis of recent reports of individuals labeled with MCI reverting to normal, Gauthier and Touchon⁶⁶ argue against the use of MCI as a clinical entity or "predementia stage of AD." Notably, a recent study by Forsberg et al.³⁰ reported that 7 of 21 MCI subjects converted to AD after 2 years, and moreover, at baseline (when adjudicated as having MCI), all 7 had PiB retention levels similar to AD subjects.

Most of the focus on MCI as a high-risk AD group has focused on the amnesic (memory impaired only) form of the disorder, originally described by Petersen and colleagues.¹³ However, depressed elders often have prominent deficits in other domains such as executive functioning or mild impairment in MCDs that may or may not include memory. In a study by Bhalla and colleagues,²⁰ approximately one-half of elderly depression patients in remission met the cognitive criteria for MCI, with most of them exhibiting the MCI-MCD subtype, some with and some without memory impairment. One may hypothesize that MCI-MCD may represent a combination of the cognitive deficits associated with late-life depression and those owing to superimposed AD neuropathology. Notably, if we examine the relative PiB retention in frontal cortex in the depressed subjects in this study by cognitive diagnosis, there is a trend toward higher PiB DVR values among those with amnesic-MCI relative to nonamnesic MCI (Fig. 3). Larger future studies will be needed to further evaluate the relationship between cognitive impairment subtyping and amyloid binding measures in elders treated for major depression.

A recent study by Rapp and colleagues⁶⁷ demonstrated that the brains of patients with AD and lifetime history of depression showed higher levels of both plaque and tangles in the hippocampus than AD patients without depression. Those AD patients with depression also had a more rapid cognitive decline than nondepressed demented subjects. Our in vivo findings are consistent with evidence that late-life depression may be either a risk factor for AD—in cases where depression may present many years before cognitive impairment—and/or a potential AD prodromal state in some individuals. Indeed, postmortem studies by Sweet et al.⁶⁸ have confirmed a predominance of AD neuropathology among well-characterized late-onset depressed patients with varying cognitive impairment who were followed longitudinally.

The heterogeneity of late-life depression and its association with cerebrovascular risk factors,⁶⁹ physiologic changes related to aging,⁷⁰ serotonergic dysfunction,⁷¹ structural brain changes,⁷² and medical burden⁷³ suggest that clinical expression of dementia may be related to a confluence of brain insults and diminished cognitive reserve. Future large prospective studies can address the relationship between the magnitude and distribution of amyloid load as measured by in vivo PET imaging and clinical and demographic factors that may contribute to the manifestation of cognitive impairment and clinical dementia. This information will likely shed further light on the complex neurobiologic mechanisms underlying depression and AD and guide future approaches to early intervention.

CONCLUSION

Our preliminary finding of heterogeneously elevated PiB retention in late-life depressed subjects with and without persistent cognitive impairment after antidepressant therapy is consistent with and supportive of the hypothesis that depression may share some common underlying neurobiologic mechanisms with the development of AD. Future studies will explore to what degree AD pathology may contribute to long-term prognosis, and also the course, and treatment response characteristics of depression in late life.

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FIGURE 1.

Representative Logan parametric PiB-PET images in 5 subjects with late-life depression who also meet criteria for MCI. A range of PiB retention in cortical areas is noted across subjects. MCI indicates mild cognitive impairment; PET, positron emission tomography; PiB, Pittsburgh Compound-B.

FIGURE 2.

Scatter plot of Logan DVR values for several cortical regions with high amyloid retention in AD [frontal (FRT), lateral temporal cortex (LTC) parietal (PAR), precuneus (PRC)], areas affected relatively later in the disease [mesial temporal cortex (MTC; including amygdala, hippocampus, and a portion of the parahippocampal gyrus), occipital (OCC), sensory motor cortex (SMC)] and comparison subcortical regions [pons (PON), subcortical white matter (SWM)] in depressed group (filled symbols) and healthy controls (open square). The open squares represent the control subjects. The filled symbols represent depressed subjects: filled square = amnesic MCI; filled triangle = nonamnesic MCI; filled circle = - cognitive normal. Bars indicate the DVR range (maximum, minimum, and mean DVR values) of AD patients previously published in Lopresti et al.²⁸ Note the large variability and overlap with AD PiB DVR values among the depressed subjects in high amyloid retention regions, particularly FRT, LTC, PAR, and PRC. AD indicates Alzheimer disease; DVR, distribution volume ratio; MCI, mild cognitive impairment; PiB, Pittsburgh Compound-B.

FIGURE 3.

Box plot showing PiB DVR values (mean, SD, and individual data points) in frontal cortex of all 8 successfully scanned depressed subjects grouped by cognitive diagnosis. Although sample sizes are small, there was a trend toward higher PiB uptake in those with amnestic MCI ($n = 3$) relative to those with nonamnestic MCI ($n = 3$). The 2 subjects with normal cognition had the lowest PiB DVR values. DVR indicates distribution volume ratio; MCI, mild cognitive impairment; PiB, Pittsburgh Compound-B.

TABLE 1

Subject Characteristics

Subject No.	Sex	Age (y)	MMSE	Education (y)	Age at Depression Onset (y)	Duration Since Depression Onset (y)	PiB DVR	
							FRT*	PCG†
Depressed								
D1	M	75	26	12	72	3	2.16	2.20
D2	M	67	29	13	33	34	1.17	1.22
D3	F	76	25	10	74	2	1.19	1.26
D4	F	72	29	13	13	59	1.26	1.20
D5	F	74	30	12	52	22	0.94	1.14
D6	M	68	29	18	54	14	1.18	1.40
D7	F	84	28	13	49	35	1.91	2.22
D8‡	F	73	28	12	24	49	—	—
D9	F	66	30	12	65	1	1.54	1.75
Controls								
C1	F	67	30	12	—	—	1.24	1.20
C2	F	69	28	19	—	—	1.71	1.95
C3	F	70	29	12	—	—	1.18	1.24
C4	F	72	30	18	—	—	1.45	1.55
C5	M	76	30	20	—	—	1.14	1.29
C6	M	75	27	18	—	—	1.18	1.20
C7	F	71	30	18	—	—	1.28	1.59
C8	F	72	29	13	—	—	1.17	1.14

* Frontal cortex.

† Precuneus.

‡ Arterial line failure.

DVR indicates distribution volume ratio; MMSE, mini-mental state examination; PiB, Pittsburgh Compound-B.

TABLE 2

Cognitive Evaluation in Depressed Subjects

Subject No.	ADRC Diagnosis	Cognitive Domains Impaired				
		Language	Visual-Spatial	Attention	Memory	
					Verbal	Visual
D1	Amnestic MCI—memory impairment plus 1 or more other domains				X	
D2	Amnestic MCI—memory impairment plus 1 or more other domains				X	X
D3	Nonamnestic MCI—multiple domains	X				
D4	Nonamnestic MCI—single domain					
D5	Normal cognition					
D6	Normal cognition					
D7	Amnestic MCI—memory impairment plus 1 or more other domains					X
D8	Nonamnestic MCI—multiple domains		X			
D9	Nonamnestic MCI—single domain					

ADRC indicates Alzheimer Disease Research Center; MCI, mild cognitive impairment.

TABLE 3
Depressed Subjects' Neuropsychologic Performance

	Mean Z-score (SD)
Speed Domain	
Digit symbol ³⁶	– 0.80 (0.87)
Grooved pegboard ³⁷	– 1.98 (3.62)
Trails A ³⁸	– 2.72 (5.61)
Visuospatial Domain	
Simple drawings ³⁹	– 0.35 (1.07)
Block design ³⁶	– 0.97 (0.89)
Clock drawing ⁴⁰	– 0.33 (0.97)
Executive Domain	
EXIT ^{41*}	– 0.71 (0.93)
Trails B ³⁸	– 1.86 (1.68)
Stroop ⁴²	– 2.2 (2.74)
WCST [†] -perseverative errors ⁴³	– 0.06 (0.42)
Language Domain	
Boston naming ³⁹	– 0.29 (1.66)
Letter fluency ⁴⁰	0.15 (0.74)
Animal fluency ⁴⁴	– 0.62 (0.83)
Spot-the-word ⁴⁵	– 0.23 (1.55)
Memory Domain	
Logical memory ⁴⁶	0.20 (1.44)
Rey-Osterreith ^{47,48‡}	– 0.64 (1.24)
CVLT ^{49§}	– 0.15 (0.87)

* Executive Interview.

[†] Wisconsin Card Sorting Test.

[‡] The original figure with several details removed to make it appropriate for geriatric subjects.

[§] California Verbal Learning Test.