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The MRI brain correlates of depressed mood, anhedonia, apathy, and anergia in older adults with and without cognitive impairment or dementia

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SUMMARY

Objectives—We examined the magnetic resonance imaging (MRI) correlates of depressed mood, apathy, anhedonia, and anergia in older adults with and without cognitive impairment or dementia.

Methods—This analysis included 270 community-dwelling older adults (59% male; 79% Caucasian; mean age 74.4 years) who were recruited into a multi-center longitudinal observational study of subcortical ischemic vascular disease (SIVD).The distribution of cognitive status included: cognitively intact (38%), cognitively impaired (27%), or demented (35%). All subjects underwent MRI and 41% were classified as having subcortical lacunes. MRI measures included cortical gray and white matter volumes, lacunar volumes in subcortical white and gray matter structures, volume of white matter hyperintensities, and total hippocampal volume. Depressed mood, anhedonia, anergia, and apathy apparent at the time of assessment were assessed using a behavioral assessment Associations between neuropsychiatric symptoms and MRI variables were evaluated using logistic regression.

Results—Subjects with neuropsychiatric symptoms were more likely to be cognitively impaired or demented than those without neuropsychiatric symptoms. In multivariate models controlling for cognitive status, age, gender, and education, higher lacunar volume in white matter was independently associated with the presence of all four neuropsychiatric symptoms.

Conclusions—We report an association between the lacunar volumes in the white matter and depressed mood, anhedonia, apathy, and anergia, thus supporting the role of subcortical ischemic vascular disease in the pathogenesis of late-life neuropsychiatric disorders.

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CONFLICT OF INTEREST
None known.

Keywords

late-life neuropsychiatric symptoms; depression; apathy; anhedonia; anergia; subcortical ischemic vascular disease; hippocampal volume; magnetic resonance imaging (MRI)

INTRODUCTION

Cerebrovascular and neurodegenerative brain changes, as well as cognitive decline commonly accompany late-life neuropsychiatric symptoms and contribute to underlying pathophysiology and heterogeneity of the disorders (Roman, 2003; Lavretsky and Chui, 2005). Subcortical ischemic vascular disease (SIVD) characterized by microvascular or small-artery disease is common in elderly patients without cognitive impairment, and in those with different types of cognitive impairment including dementia. SIVD is thought to be responsible for a certain pattern of cognitive impairment with predominant executive dysfunction, and for the development of depression and other behavioral symptoms (Roman *et al.*, 2002; Chui, 2005). Magnetic resonance imaging (MRI) is more sensitive than the clinical examination to detect subcortical lacunes and deep white matter changes that do not present with focal neurological signs, but might result in cognitive or neuropsychiatric symptoms due to disruption of cortical–subcortical pathways (Roman *et al.*, 2002; Roman, 2003; Chui, 2005; Lavretsky and Chui, 2005).

Differentiating among symptoms of depressed mood, apathy, anhedonia, or anergia is sometimes difficult because of the overlap in clinical features (Marin, 1997; WHO, 2003). The use of MRI may shed light on neurobiology and differences in neurocircuitry involved in the mediation of mood and motivational impairment in late life (Hussain *et al.*, 1991; Coffey *et al.*, 1993; Krishnam *et al.*, 1997; Alexopoulos *et al.*, 1997a; Kumar *et al.*, 1998; Steffens *et al.*, 1999; Lampe *et al.*, 2001; Greenwald *et al.*, 2001; Sackeim, 2001; Taylor *et al.*, 2003; Lampe and Heeren, 2004; O'Brien *et al.*, 2004; Baldwin, 2005). Neuroanatomical abnormalities consistently identified in patients with late-life major depression include smaller brain volumes and larger volumes of high intensity lesions in the subcortical gray and white matter (Lavretsky and Chui, 2005). Structural atrophy has been reported in the prefrontal cortex (Buchsbaum *et al.*, 1984; Baxter *et al.*, 1989; Martinot *et al.*, 1990; Bench *et al.*, 1992; Biver *et al.*, 1994; Mann *et al.*, 1996; Drevets *et al.*, 1997; George *et al.*, 1997; Drevets, 2000; Tekin and Cummings, 2002) and hippocampus (Mayberg *et al.*, 1990, 1992; Larisch *et al.*, 1997; Mayber *et al.*, 1997; Liotti *et al.*, 2002). Historically, neuroimaging studies of stroke have focused on lesion-behavior relationships (Tatemichi *et al.*, 1995; Okada *et al.*, 1997; Andersson *et al.*, 1999; Van Der Werf *et al.*, 1999; Piamarta et al., 2004; Yamagata *et al.*, 2004). A few studies have identified neuroanatomical correlates of behavioral symptoms in patients with dementia of the Alzheimer's type (Sultzer *et al.*, 1995; Sultzer, 1996; Holthoff *et al.*, 2005; Mega *et al.*, 2005).

The objectives of this report were to examine the relation between four common late-life neuropsychiatric symptoms and MRI volumetric measures of lacunes and white matter signal hyperintensities, cortical gray and white matter, and hippocampus. We hypothesized that neuroanatomical measures of subcortical ischemic vascular disease would contribute to all four neuropsychiatric symptoms, independently of MRI measures of cortical gray and white matter and hippocampal volumes. Although several studies have tried to identify the relationship of subcortical vascular disease and depression or apathy, none of the findings related to lesion laterality or localization have been consistently replicated (Manes *et al.*, 1999; Piamarta et al., 2004; Vataja *et al.*, 2004; Brodaty *et al.*, 2005).

No prior studies have attempted to differentiate the MRI correlates of depressed mood, apathy, anergia, and anhedonia in the same clinical sample.

METHODS

Subjects were recruited to participate in a multi-center study examining contributions of subcortical ischemic vascular disease (SIVD) to cognitive impairment and dementia in a longitudinal study. Four clinical sites from three academic dementia centers participated: the University of Southern California (USC) site recruited 50 subjects; the University of California, San Francisco site recruited 38 subjects, the University of California, Davis (Sacramento and Martinez) sites recruited 182 subjects. All sites but the USC used the same MRI scanner. Subjects were patients who presented to dementia clinics seeking evaluation for cognitive problems or were found to have cerebrovascular disease. Cognitively normal subjects were recruited from the community. Exclusionary criteria at time of enrollment included age < 55, non-English-speaking, cortical strokes, and severe illnesses (other than cerebrovascular disease or dementia) or medications likely to affect cognition.

Participants received a comprehensive clinical evaluation that included a detailed medical and neurological history and examination, appropriate laboratory tests, and neuropsychiatric assessment of behavioral and psychological symptoms. Cognition was evaluated using a previously reported battery of neuropsychological tests (administered as part of larger study sample, but not presented here) (Mungas *et al.*, 2001; Kramer *et al.*, 2002). Participants were diagnosed at a multidisciplinary case conference. Dementia was diagnosed by DSM-IV criteria (Martinot *et al.*, 1990). Subjects with cognitive impairments not severe enough to meet dementia criteria, or those who evidenced no functional impairment, were diagnosed as having cognitive impairment without dementia. Demented subjects were further clinically diagnosed using the National Institute of Neurological and Communicative Disorders and Stroke (NINDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) diagnostic criteria for AD, and California Alzheimer's Disease Diagnostic and Treatment Center (ADDTC) criteria for ischemic vascular dementia (IVD) (Chui *et al.*, 1992, 2000). Interrater reliability in the clinical diagnosis of IVD ranged from kappa 0.30–0.61 depending on the diagnostic criteria used (Chui *et al.*, 2000). The presence and the severity of comorbid cardiovascular conditions (current and past) was assessed by a standard instrument using direct and different sources of information (e.g. subjects, family members, medical records). The Institutional Review Boards at all participating institutions approved this study, and all subjects or their representatives gave written informed consent to participate in the study.

The presence of lacunes was determined by an expert-radiologist who reviewed all MRI scans. Clinical diagnoses of demented subjects with lacunes included possible or probable ischemic vascular dementia (n = 16; 42%), mixed AD/vascular disease (n = 10; 26%), and possible or probable AD (n = 11; 29%) and cerebrovascular disease (n = 1; 3%). Clinical diagnoses of demented subjects without lacunes included probable or possible AD (n = 42; 76%), probable or possible ischemic vascular dementia (n = 3; 5%), mixed AD/vascular disease (n = 5; 9%), cerebrovascular disease (n = 3; 5%), frontal temporal lobe degeneration (n = 1; 2%), and possible dementia with Lewy bodies (n = 1; 2%). Clinical diagnoses were not used in the analyses reported in this paper. Demographic characteristics and global cognitive function (measured by the Mini-Mental State Examination [MMSE]) are presented by cognitive group (unimpaired, cognitively impaired, and demented) in Table 1.

Neuropsychiatric assessment

Behavioral ratings were based upon clinician ratings using the Psychiatric Evaluation section of the Minimum Uniform Dataset (MUDS) of the California Alzheimer's Disease Centers Program administered at baseline. Central training on uniform administration of the MUDS

was provided as part of the Alzheimer's Disease Centers Program (Victoroff *et al.*, 1997). Symptom ratings were made separately for depressed mood, apathy, anhedonia or anergia based on severity, as follows: 0 = not present, 1 = questionable; 2 = present, but mild at subthreshold/subsyndromal level; 3 = present and severe at threshold/syndromal level; or 4 = not determined. The evaluators assessed at the time of evaluation whether participants had depressed mood, anhedonia, apathy or anergia and whether the severity of these symptoms achieved either syndromal or subsyndromal level. The assessment of each of these neuropsychiatric behaviors was based on the patient and caregiver report, and direct clinical examination. Victoroff and colleagues (1997) determined the reliability of caregiver ratings and compared caregiver ratings with clinician ratings of all types of behavioral disturbances. Caregiver and clinical inter-rater reliability was highest for depression and lowest for psychosis ranging between r 0.2 and 0.9. In our analyses, we combined both syndromal and subsyndromal severity of neuropsychiatric symptoms to reflect clinically significant psychopathology that is likely to have a comparable effect on functional impairment (Lavretsky and Kumar, 2002). The reference group consisted of subjects with no such symptoms or with 'questionable' symptoms. The percentage of subjects with clinically significant symptoms by cognitive recruitment group are presented in Table 1.

MRI methods

MR image acquisition and segmentation methods have been previously reported (Fein *et al.*, 2000; Du *et al*., 2005). MRI variables of interest were computerized measures of volumes of white matter signal hyperintensities (WMH), cortical gray matter (cGM), white matter (WM), total hippocampal volume (HV), and volume of lacunes within specific structures: thalamus, putamen, caudate, globus palli- dus, and white matter. Subcortical lacunes were small (>2 mm) areas of the brain with increased signal relative to CSF on proton density MRI in subcortical gray and white matter seen in axial slices at the level of basal ganglia and thalamus. Lacunes were differentiated from perivascular spaces, which can be particularly prominent below the anterior commissure and putamen and at bends in the course of penetrating arterioles. WMH volumes were assessed based on semi-automatic segmentation using T1-, proton density- and T2-weighted images together. WMH was defined as regions that are hyperintense on proton density- and T2-weighted images and are anatomically located in white matter (WM) region. When appearing in WM, lacunes were differentiated from WMH by an isointense signal to CSF and lesion size ranging from 3–15 mm. To differentiate lacunes in the white matter and WMH, only cystic lacunes were included. In the subcortical gray matter, a more liberal definition was used for lacunes (i.e. discrete hyperintensities > 2 mm in diameter on proton density images). Hippocampal boundaries were defined using the protocol described by Watson including the hippocampus proper, dentate gyrus, subiculum, fimbria, and alveus (Du *et al*., 2005). All volumes were expressed as a percent of total intracranial volume (ICV) that was measured from the top of the brain to the slice where the cerebral peduncles appeared. In repeated ratings, intraclass correlation coefficients (n = 10) were 0.93 for percent of white matter; 0.99 for percent of white matter signal hyperintensities; 0.95 for cortical gray matter; 0.99 for sulcal CSF; 0.99 for ventricular CSF (Fein *et al.*, 2000). Inter-rater reliability for hippocampus was determined by marking hippocampus of ten subjects twice and expressing the coefficients of variation, which was 1.0% (Du *et al.*, 2005).

Data analysis

Univariate and multivariate logistic regression models were used for each neuropsychiatric symptom. In these analyses, the presence or absence of clinically-significant neuropsychiatric symptoms were evaluated in relation to cognitive group (normal, cognitively impaired, demented), age, gender, ethnicity, the presence of lacunes (present or absent), the volumes of lacunes in the white matter and subcortical gray matter structures, WMH, HV, cGM, and WM.

To consider the multiple hypothesis testing in light of the fact that this was an exploratory analysis, the significance level adopted was alpha = 0.01 (two-tailed).

Associations between the independent variables and the presence of neuropsychiatric symptoms were summarized as Odds Ratios (OR) and 95% Confidence Intervals (CI). The reference groups for gender, ethnicity, cognitive group and lacunes are male, white, not cognitively impaired, and 'no lacunes', respect- ively. Because the scale of measurement for lacunar volume was so small, all MRI volumetric measures of lacunar volume were divided by 0.03 (the SD of the total lacunar volume) to improve the interpretability of the OR. Therefore, the OR for these variables represent the OR per 0.03% of intracranial volume. For similar reasons, the OR for HV were expressed per SD (0.07% of intracranial volume). OR for all other MRI variables were expressed per unit of the variable (i.e. per unit percentage of intracranial volume).

Because our major hypotheses related to the associations of subcortical ischemic vascular disease to these neuropsychiatric symptoms, our multivariate logistic regression modeling took the following approach. Only MRI variables that were significant at $p < 0.01$ on univariate analyses were considered in multivariate models for a given neuropsychiatric symptom. At each step in the modeling approach described below, only MRI variables that remained significant at $p < 0.01$ in the adjusted models were retained. After forcing in cognitive groups, age, gender, and education as covariates, we first tested the significance of the lacunar volume in the white matter and subcortical gray matter structures. We then tested whether WMH, as another measure of vascular disease, remained significantly related to the neuropsychiatric symptom, after adjustment for cognitive group, demographic variables, and the significant lacunar volume variables. In the last step, we tested whether WM, cGM and HV were significantly related to the neuropsychiatric symptom with adjustment for cognitive group, demographics, and the multivariately significant lacunar volume and WMH variables. To determine if the observed MRI associations might be confounded by vascular disease, we adjusted for vascular conditions (stroke, hypertension, hyperlipidemia, diabetes, congestive heart failure, myocardial infarction, coronary bypass surgery), presence of stroke-related hemiparesis, ataxia, or extrapyramidal signs, as well as a measure of activities of daily living (ADL) (Blessed-Roth Dementia Rating Scale) (Blessed *et al.*, 1988).

For each subject, we also computed a summary global behavioral measure of neuropsychiatric symptoms. This summary variable was the total number of neuropsychiatric symptoms rated as present, and ranged from 0–4. For this global behavioral measure, we conducted an ordinal logistic regression. The dependent ordinal variable was the number of neuropsychiatric symptoms present. The independent variables and modeling approach followed those described above.

RESULTS

Two hundred seventy volunteers, 160 men (59.3%) and 110 women (40.7%) were evaluated at baseline and diagnosed as cognitively intact ($n = 103$, 38.2%), cognitively impaired ($n = 74$, 27.4%), or as having dementia ($n = 93$, 34.4%). One hundred and twelve subjects (41.5%) were determined to have lacunes. The majority of subjects ($n = 214$, 79.3%) were Caucasian, and the mean age of the sample was 74.6 years (range 52–94 years). Table 1 describes the demographic and clinical characteristics of the sample.

In the entire sample, 49 subjects (18.1%) were rated with clinically significant depressed mood, 34 (12.7%) were rated to have anhedonia, 71 (26.3%) had anergia, and 49 (18.2%) had apathy. As expected, we observed some degree of overlap in symptoms, i.e. 20 (40.8%) subjects with depressed mood had anhedonia, 36 (73.5%) had anergia, and 20 (40.8%) had apathy. Table 2

presents the results of the univariate logistic regression for each of the four neuropsychiatric symptoms. Associations significant at $p < 0.01$ are bolded in the table. To summarize, all four symptoms, depressed mood, anhedonia, anergia, and apathy were significantly more prevalent among subjects who were demented, while anergia and apathy were also more prevalent among cognitively impaired subjects, relative to unimpaired subjects. Neither age nor gender were associated with the presence of symptoms.

All four symptoms were associated with higher total volume of lacunes, as well as larger volume of lacunes in the white matter and in putamen. The presence of anhedonia, anergia, and apathy was also associated with smaller white matter volume. Smaller cortical gray matter volume was associated with anergia and apathy. A greater lacunar volume in the thalamus was associated with depressed mood. A greater volume of white matter hyperintensities was associated with anergia and anhedonia. Smaller hippocampal volume was associated with apathy only. Despite our presentation of the multivariate analyses in Table 3, we chose also to present the univariate results to be able to compare to other studies that did not adjust for other confounding variables.

Bivariate Pearson correlation coefficients among the MRI variables demonstrated weak-to-moderate correlations. Negative correlations were observed between the lacunar and white matter hyperintensities volumes and the white matter (correlations ranging from 0.1 to −0.26) and gray matter (correlations ranging from −0.04 to −0.49) volumes (Du *et al.*, 2005).

Table 3 presents the results of the multivariate logistic regression adjusting for age, gender, education, and cognitive status. Adjustment for race did not change our results. Greater lacunar volume in the white matter and the diagnosis of dementia were associated with the presence of neuropsychiatric symptoms. After lacunar volume in the white matter was entered into the model, no other MRI variable was significantly associated with any neuropsychiatric symptom. In general, adjustment for each of the vascular conditions listed in Table 1 (stroke, hypertension, hyperlipidemia, diabetes, congestive heart failure, myocardial infarction, coronary bypass surgery), the presence/absence of stroke-related hemiparesis, ataxia or extrapyramidal signs, and Blessed-Roth ADL score did not appreciably alter the odds ratios associated with the MRI variables (data not shown). For the anergia outcome, the estimate of association of lacunar volume in white matter was somewhat reduced with adjustment for a history of stroke (stroke-adjusted OR = 1.35, $p = 0.03$).

We did not find any significant interactions between cognitive status and MRI variables (data not shown), indicating that these MRI associations did not vary by cognitive status. We also repeated our multivariate analyses, confined to unimpaired subjects only. Although the results were in general not statistically significant due to small sample size, in all cases, the magnitude of the odds ratios (evaluating MRI associations with symptoms) were completely consistent with those reported in the total sample.

After combining all behavioral symptoms into a single global variable, 161 (60%) subjects had none of the four neuropsychiatric symptoms, 49 (18%) were positive on one symptom, 26 (10%) were positive on two symptoms, 18 (7%) were positive on three symptoms, and 12 (5%) subjects were positive on all four symptoms. In the univariate ordinal logistic regression analyses, all of the MRI variables (except for the lacunar volume in globus pallidus) were significantly associated with the presence of neuropsychiatric symptoms. However, in the multivariate analysis adjusting for cognitive status, age, gender and education, only the white matter lacunar volume was significantly associated with the global behavioral measure (OR = 1.63 per 0.03%, 95% CI 1.31, 2.02, $p < 0.0001$).

DISCUSSION

The major findings of this study included: (1) the presence of neuropsychiatric symptoms was associated with the level of cognitive impairment and the volume of lacunes; and (2) lacunar volume in white matter was associated with each individual symptom as well as the global measure of neuropsychiatric symptoms. Although other structural changes (e.g. cortical gray matter volume or hippocampal volume; lacunar volume in the thalamus or in the globus pallidus) were associated with behavioral symptoms in the univariate analyses, the statistical significance was not maintained in the multivariate analyses. Overall, these findings support the role of cerebrovascular disease in the pathogenesis of late-life depression, and other mood and motivational disturbances. In addition, reduced white matter volume appears important in the pathophysiology of motivational and energy disturbances supporting the role of disrupted or reduced brain connectivity in late-life neuropsychiatric disorders (Lavretsky and Kumar, 2001).

The link with cerebrovascular damage to neural circuits and nuclei that mediate mood and behavior via compromising frontostriatal pathways has been long established (Lavretsky and Kumar, 2001; Kumar and Cook, 2002; Lavretsky and Chui, 2005). Subcortical dementias, including vascular type, are more likely to result in depression than cortical dementias (Sobin and Sackeim, 1997). The relevance of cortical-subcortical connections was demonstrated by Sultzer and colleagues who reported that cortical metabolic dysfunction identified by PET scans in vascular dementia patients was related to subcortical ischemic lesions identified on MRI (Starkstein *et al.*, 1995). Moreover, development of depression is more likely to occur in Alzheimer's patients with subcortical atrophy (Starkstein *et al.*, 1995). Along with clinical observations, structural neuroimaging studies have noted low volumes of structures of the frontostriatal pathways in neurologically unimpaired depressed patients, including the subgenual anterior cingulate (Drevets *et al.*, 1997), caudate head (Krishnan *et al.*, 1992) and the putamen (Husain *et al.*, 1991). Low volumes of the anterior cingulate, the orbitofrontal cortex and the rectus gyrus (Ballmaier *et al.*, 2004) and hyperintensities in subcortical structures and their frontal connections are also prevalent in geriatric depression (Coffey *et al.*, 1990; Krishnan *et al.*, 1997; Steffens *et al.*, 1999). Overall, these findings support the role of the disrupted fronto-striatal integrity as a feature of late-life depression with or without dementia.

Apathy is also known to be associated with cerebrovascular disease, as it occurs after stroke and is related in large degree to lesion location (Marin, 1990; Cummings, 1993; Starkstein *et al.*, 1993; Marin, 1996; Duffy and Kant, 1997; Marin, 1997; Okada *et al.*, 1997; Finset and Andersson, 2000). Motivational circuitry of the brain includes such important structures as the nucleus accumbens, ventral pallidum, and ventral tegmental area with projections to the amygdala, hippocampus, basal ganglia, motor cortex, and anterior cingulate. A more profound state of psychomotor retardation and apathy, or abulia (Fisher, 1983), can result from strokes that disrupt frontosubcortical pathways, such as anterior cingulate and capsular lesions (Duffy and Kant, 1997; Lavretsky *et al.*, 1999, 2007). In our sample, the most highly significant MRI correlates of apathy on univariate analysis were greater volumes of lacunes in the white matter and lower white and cortical gray matter volumes. Multivariately, only lacunar volume in the white matter was related to the presence of apathy. Although we found inverse associations between hippocampal volume and apathy in the unadjusted analyses (Table 2), this association was not apparent in multivariate models, possibly due to controlling for cerbrovascular disease.

Only limited data are available addressing neuroanatomical correlates of apathy, anhedonia, and anergia (Krishnan *et al.*, 1997; Lampe *et al.*, 2001; Lavretsky and Kumar, 2001; Kumar and Cook, 2002; Lampe and Heeren, 2004; Piamarta et al., 2004). It would be important to continue examining these relationships in different clinical populations using standardized

volumetric approaches combined with the analyses of the white matter integrity and hippocampal atrophy.

Although other factors are known to contribute to late-life depression and other neuropsychiatric symptoms, such as various life stressors or comorbid medical conditions (Krishnan *et al.*, 2002; Alexopoulos, 2005), we did not find a significant contribution of medical comorbidity to depressed mood nor to other neuropsychiatric symptoms.

The limitations of our study include the use of a generic assessment of neuropsychiatric symptoms on the basis of the MUDS assessment and the categorical diagnostic approach. Thus, we were not able to measure the severity of the symptoms. The results of the study are based on a cross-sectional analysis of a large convenience sample with incidental occurrence of neuropsychiatric symptoms. Behavioral assessment did not include the use of standard rating scales measuring the severity of symptoms. We combined subjects with syndromal and subsyndromal severity of neuropsychiatric symptoms. We observed some overlap in the behavioral symptoms, but examined each symptom individually in addition to using a global behavioral measure. This approach carries limitations of going outside the accepted validated syndrome of depression into the new area of refining behavioral symptoms. However, this may also be viewed as an opportunity to explore new approaches to identifying the MRI correlates underlying these neuropsychiatric symptoms. These symptoms are frequently lumped together in depressive disorders despite the difference in the presentation resulting in heterogeneity of clinical samples that stalls progress in research on understanding biological substrates of depression and other neuropsychiatric symptoms and syndromes. Therefore, our findings are preliminary due to the limitations in the assessment instruments that we used to identify behavioral symptoms and will require replication using validated scales.

We did not control for the use of psychotropic medication among patients in this cohort, which might have an additional effect on structural changes (Lavretsky *et al.*, 2005) or for personal or family history of a depressive disorder (Morris *et al.*, 1992). Finally, we did not detail the patterns of cognitive impairment associated with neuropsychiatric symptoms or with structural brain changes.

Despite these limitations, our results are intriguing and warrant further investigation. The search for the neurobiological substrates of neuropsychiatric symptoms supports the use of neuroimaging as a tool for developing a neurocircuitry based classification of late-life neuropsychiatric disorders(Alexopoulos *et al.*, 2005). Understanding the neuroanatomical characteristics of symptoms of depression, apathy, anhedonia, and anergia in older subjects may help develop more homogeneous behavioral endophenotypes in subjects with and without cognitive impairment, which might guide symptom-specific drug development.

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Table 1

Demographic, clinical, and MRI characteristics by cognitive groups

Variable	Cognitively normal (*n* = 103)	Cognitively impaired (*n* = 74)	Demented (*n* = 93)	*P*-value*
N				
Age	73.6(7.6)	74.4(8.1)	76(8.6)	0.12
Education	15.1(3.1)	14.5(3.1)	13.4(3.6)	0.002
MMSE	29.1(1.4)	27.2(2.6)	20.3(5.3)	<0.0001
Gender				
Male	53(51.5)	56(75.7)	51(54.8)	0.003
Female	50(48.5)	18(24.3)	42(45.2)	
Race				
White	86(83.5)	55(74.3)	73(78.5)	0.36**
African-American	5(4.9)	3(4.1)	3(3.2)	
Hispanic	4(3.9)	9(12.2)	11(11.8)	
Asian	8(7.8)	7(9.5)	6(6.5)	
Depression	9(8.7)	17(23)	23(24.7)	0.01
Anhedonia	5(5)	9(12.2)	20(21.7)	0.002
Anergia	10(9.7)	19(25.7)	42(45.2)	<0.0001
Apathy	2(1.9)	12(16.4)	35(37.6)	<0.0001
Stroke	16(17.2)	22(32.4)	13(14.9)	0.02
Hypertension	40(43)	36(52.9)	43(49.4)	0.44
Myocardial infarction	3(3.2)	10(14.7)	10(11.5)	0.03
Coronary Artery Bypass Graft Surgery	6(6.5)	8(11.8)	7(8)	0.48
Arrhythmia	12(12.9)	4(5.9)	14(16.1)	0.15
Congestive heart failure	3(3.2)	7(10.3)	4(4.6)	0.16**
Hyperlipidemia	23(24.7)	28(41.2)	22(25.3)	0.04
Diabetes	9(9.7)	15(22.1)	6(6.9)	0.01
MRI variables				
%Cortical Gray matter	39.1(2.6)	37.3(3.1)	35.3(3.2)	<0.0001
%White matter	35.6(2.8)	34.0(2.7)	33.0(2.9)	<0.0001
%Hippocampal volume	4.9(0.6)	4.1(0.7)	3.6(0.8)	<0.0001
%White Matter Signal Hyperintensities (WMSH)	0.7(1)	1.4(1.4)	2.0(2.2)	<0.0001
%Lacunar volume- Caudate	0.2(0.9)	0.1(0.2)	0.1(0.4)	0.76
%Lacunar volume- Globus Pallidus	0.07(0.29)	0.05(0.15)	0.05(0.19)	0.80
%Lacunar volume- Putamen	0.2(0.8)	0.6(1.4)	0.3(1.0)	0.06
%Lacunar volume- Thalamus	0.1(0.4)	0.4(0.8)	0.3(0.8)	0.02
% Lacunar volume- White Matter	0.2(0.5)	0.8(1.9)	0.4(1.2)	0.004
%Lacunar volume-Total	0.7(2.0)	1.9(3.3)	1.2(2.6)	0.01

* Data are presented as mean (SD) with group comparisons by ANOVA for continuous variables; data are presented as number (%) with group comparisons by chi-square for categorical variables.

** *p*-value from Fisher's exact test.

Table 2

Univariate logistic regression analyses of the association between neuropsychiatric symptoms, demographic factors, cognitive status, and MRI regional volumes*

	Depression OR (95% CI); *p*	**Anhedonia OR (95% CI); *p***	**Anergia OR (95% CI); *p***	**Apathy OR (95%CI); *p***
Age (years)	1.01 (0.95; 1.05); 0.51	0.99 (0.97,1.04); 0.97	0.99 (0.97; 1.04); 0.93	0.99 (0.96; 1.04); 0.93
Gender(female)	1.36 (0.73,2.54); 0.33	0.79 (0.37,1.68); 0.54	1.36 (0.73,2.54); 0.33	0.99 (0.53,1.87); 0.99
African-American	1.39 (0.95,6); 0.06	1.87 (0.64,5.44); 0.25	2.12 (0.89,5.04); 0.09	7.25 (2.97, 17.66); 0.0001
Hispanic	1.06 (0.22,5.12); 0.94	0.71 (0.09,5.79); 0.79	0.49 (0.14,1.74); 0.27	1.36 (0.28,6.62); 0.70
Asian	0.5 (0.11,2.26); 0.37	0.75 (0.16,3.4);0.71	1.69 (0.48,6.01); 0.42	1.53 (0.48, 4.9); 0.47
Education (years)	0.94 (0.86,1.03);0.19	0.88 (0.79,0.98); 0.02	0.94 (0.87,1.02); 0.13	**0.85 (0.77, 0.94); 0.002**
Cognitive group Cognitively impaired	3.11 (1.3, 7.45); 0.011	2.66 (0.85, 8.3); 0.09	**3.21 (1.39, 7.41); 0.006**	**9.93 (2.15, 45.9); 0.003**
Demented	**3.43 (1.5,7.87); 0.004**	**3.43 (1.91, 14.89); 0.001**	**7.66 (3.55, 16.53); 0.0001**	**30.47 (7.07, 131.38); 0.0001**
Cortical gray matter volume	0.95 (0.87, 1.04);0.25	0.90 (0.81,1); 0.04	**0.88 (0.81, 0.96); 0.003**	**0.80 (0.73, 0.88); 0.0001**
White matter volume	0.88 (0.79, 0.98) 0.022	**0.84 (0.74, 0.96); 0.008**	**0.83 (0.75, 0.92); 0.0001**	**0.81 (0.72, 0.91); 0.0001**
Lacunes present	2.17 (1.16, 4.07); 0.015	2.52 (1.2, 5.28);0.014	**3.14 (1.7, 5.5); 0.0001**	1.99(1.06, 3.71);0.031
Lacunar volume	**1.23 (1.11, 1.35); 0.0001**	**1.26 (1.13, 1.39); 0.0001**	**1.23 (1.11, 1.35); 0.0001**	**1.21 (1.09, 1.33); 0.0001**
White matter signal hyperintensities	1.14 (0.96,1.35); 0.13	**1.31 (1.09, 1.56); 0.004**	**1.35 (1.15, 1.59); 0.0001**	1.19 (1.01,1.4); 0.041
White matter lacunar volume	**1.52 (1.2, 1.93); 0.001**	**1.49 (1.18, 1.88); 0.001**	**1.44 (1.14, 1.81); 0.002**	**1.50 (1.19, 1.9); 0.001**
Caudate lacunar volume	1.18 (0.8, 1.73); 0.41	1.31 (0.88, 1.96); 0.18	1.18 (0.8, 1.73); 0.41	1.19 (0.81, 1.75); 0.38
Globus pallidus lacunar volume	1.56 (0.48, 5.11); 0.46	3.12 (0.99, 9.85); 0.05	1.56 (0.48, 5.11); 0.46	1.46 (0.44, 4.86); 0.54
Putamen lacunar volume	**1.39 (1.09, 1.76); 0.007**	**1.57 (1.22, 2.02); 0.0001**	**1.39 (1.09, 1.76); 0.007**	**1.45 (1.14, 1.85); 0.003**
Thalamus lacunar volume	**1.95 (1.28, 2.96); 0.002**	1.59 (1.07,2.36); 0.021	1.65 (1.12, 2.45); 0.012	1.36 (0.93, 1.98); 0.11
Hippocampal volume	0.82 (0.58, 1.17); 0.27	0.69 (0.46, 1.03); 0.07	0.76 (0.56, 1.03); 0.07	**0.54 (0.38, 0.77); 0.001**

For MRI variables, odds ratios are expressed per unit (% of total intracranial volume) except for: lacunar volumes, odds ratios expressed per 0.03 (approximate SD); hippocampal volume, odds ratios expressed per 0.07 (approximate SD). Associations significant at $p < 0.01$ are bolded.

Table 3

Hypothesis-driven multivariate logistic regression adjusting for cognitive status, age, gender and education

	Depression			Anhedonia			Anergia			Apathy		
	OR	**95%CI**	***p*-value**	**OR**	**95%CI**	***p*-value**	**OR**	**95%CI**	***p*-value**	**OR**	**95%CI**	***p*-value**
Cognitively impaired	2.48	(0.97, 6.36)	0.06	1.6	(0.47, 5.47)	0.45	2.22	(0.91, 5.38)	0.08	6.66	(1.36, 32.52)	0.019
Demented	2.97	(1.23, 7.14)	0.015	4.2	(1.44, 12.23)	**0.009**	7.21	(3.25, 16.01)	<**0.0001**	26.17	(5.95, 115.07)	<**0.0001**
Age at baseline (years)	1.02	(0.98, 1.07)	0.29	1.01	(0.96, 1.06)	0.72	1.01	(0.97, 1.04)	0.77	1.00	(0.96, 1.04)	0.92
Gender (female)	1.82	(0.9, 3.7)	0.10	0.82	(0.35, 1.88)	0.63	0.71	(0.37, 1.35)	0.29	1.12	(0.52, 2.39)	0.77
Education (years)	1.00	(0.9, 1.11)	0.99	0.94	(0.84, 1.06)	0.30	1.00	(0.92, 1.1)	0.97	0.93	(0.83, 1.03)	0.18
%Lacunar volume - white matter	1.67	(1.25, 2.23)	**0.0005**	1.53	(1.16, 2.01)	**0.002**	1.53	(1.15, 2.03)	**0.003**	1.59	(1.18, 2.15)	**0.002**

*After forcing in cognitive status, age, gender, and education, only significant predictors at $p < 0.01$ are included. For lacunar volumes, OR expressed per 0.03 (approximate SD).