RESEARCH ARTICLE

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The external validity of MRI-defined vascular depression

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Objective: Multiple diagnostic criteria have been used to define vascular depression (VD). As a result, there are discrepancies in the clinical characteristics that have been established for the illness. The aim of this study was twofold. First, we used empirically established diagnostic criteria to determine the clinical characteristics of magnetic resonance imaging (MRI)-defined VD. Second, we assessed the agreement between a quantitative and qualitative method for identifying the illness.

Method: We examined the baseline clinical and neuropsychological profile of 38 patients from a larger, double-blind, randomized, 12-week clinical trial comparing nortriptyline with sertraline in depressed older adults. Ten patients met quantitative criteria for MRI-defined VD based on the highest quartile of deep white matter hyperintensity (DWMH) volume. Fourteen patients met qualitative criteria for MRI-defined VD based on a DWMH score of 2 or higher on the Fazekas' modified Coffey rating scale.

Results: Age, gender, cumulative illness rating scale-geriatric (CIRS-G) score, two measures of psychomotor retardation [the psychomotor retardation item of the Hamilton Rating Scale for Depression (HRSD) as well as performance on the Purdue Pegboard], and performance on the Stroop Color/Word test (a measure of the response inhibition component of executive functioning) were significantly different between those with VD and non-VD.

Conclusions: Patients with VD have a distinct clinical and neuropsychological profile that is mostly consistent across different methods for identifying the illness. These findings support the notion that MRI-defined VD represents a unique and valid subtype of late-life depression. Copyright © 2013 John Wiley & Sons, Ltd.

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Introduction

The vascular depression (VD) hypothesis proposes that cerebrovascular disease may contribute to the development of late-life depression (Krishnan and McDonald, 1995; Alexopoulos *et al.*, 1997b). This hypothesis originated from findings that patients with late-onset depression had higher rates of hyperintensities on T2-weighted brain magnetic resonance imaging (MRI) than patients with early-onset depression (Hickie *et al.*, 1995; Salloway *et al.*, 1996; Krishnan *et al.*, 1997). Moreover, the presence and severity of hyperintensities in depressed older adults was associated with greater neuropsychological impairment (e.g., deficits in executive functions and processing speed) (Lesser *et al.*, 1996; Salloway *et al.*, 1996; Alexopoulos *et al.*, 1997a) and poor response to antidepressant treatment (Hickie *et al.*, 1995; Alexopoulos *et al.*, 2008; Sheline *et al.*, 2010). On the basis of these findings, a coherent theory of VD emerged in which late-life depression was seen as a consequence of structural damage to corticostriatal circuits secondary to cerebrovascular disease (Alexopoulos *et al.*, 1997a; Steffens and Krishnan, 1998).

Enthusiasm for the construct led a number of researchers to propose diagnostic criteria for VD (Alexopoulos *et al.*, 1997b; Krishnan *et al.*, 1997; Steffens and Krishnan, 1998; Krishnan *et al.*, 2004). In one study, patients with VD were identified as those with a first onset of depression at 60 years of age or older and a vascular score of 1 or higher on the cumulative illness rating scale-geriatrics (CIRS-G). The illness was associated with cognitive impairments in fluency and naming, psychomotor retardation, lack of insight, and limited depressive ideation (Alexopoulos *et al.*, 1997b). In another study, patients with VD were identified based on the presence of either deep white matter or subcortical gray matter hyperintensities rated on a qualitative scale. VD was associated with a late age of onset, lower rate of family psychiatric history, and greater rates of anhedonia and functional disability (Krishnan *et al.*, 1997). A subsequent study used a similar definition of VD. These patients were older, had a later age of illness onset, less prevalence of a family history of mental illness, a lower risk of decreased libido, and an increase in lassitude, psychomotor retardation, psychomotor agitation, and functional disability when compared with patients with non-VD (Krishnan *et al.*, 2004). As a result of the different definitions used to identify VD, the discrepant findings across these studies are difficult to interpret (Sneed *et al.*, 2006).

In order to establish VD as a unique subtype of depression in late-life, Sneed *et al.*, (2006) assessed the validity of the diagnosis. Data from two, large clinical samples of late-life depressed patients were used to conduct a latent class analysis. The results demonstrated that patients could be divided into a VD and a non-VD group based on the presence or absence of lesions in the deep white and subcortical gray matter, executive dysfunction, and late age-at-onset (Sneed *et al.*, 2008b). Deep white matter hyperintensity (DWMH) burden identified the VD group with the greatest precision, making it the only indicator necessary to determine class membership. These findings provide the first empirical evidence for the validity of MRI-defined VD and the first empirically based diagnostic criteria for the illness.

Given a valid definition, the next step to establishing VD as a distinct diagnostic subtype is to determine the clinical characteristics of the illness. VD has consistently been associated with poor response to antidepressant treatment. In one study, patients who failed to respond to antidepressant medication had significantly greater hyperintensity burden than responders and non-depressed older adults (Gunning-Dixon *et al.*, 2010). In another study, 38 patients were classified as vascular depressed if their DWMH volume ratings were in the highest quartile of the distribution. None of the 10 patients classified as VD responded to medication treatment (Sneed *et al.*, 2011). In contrast to the qualitative ratings used to define VD in previous studies, these studies used a semi-quantitative approach for the assessment of hyperintensities. It is unclear whether these methods identify the same patient population, and furthermore, whether this population is characterized by the same clinical profile.

The aim of this study was to assess the clinical characteristics of MRI-defined VD using both a qualitative and quantitative method for the assessment of DWMH burden. A further aim of this study was to estimate the agreement in diagnosis of MRI-defined VD between these two approaches. With regard to the clinical characteristics of VD, we hypothesized that patients with MRI-defined VD would have increased rates of anhedonia, psychomotor retardation, lassitude, and feelings of guilt as well as a later age-at-onset of depression and a low rate of family history of mental illness compared with patients with non-VD. We also expected patients with MRI-defined VD to demonstrate greater neuropsychological impairment than patients with non-VD, particularly in domains mediated by frontal networks (i.e., executive functioning and psychomotor speed).

Method

Procedure

This study was a double-blind, randomized, 12-week clinical trial comparing nortriptyline to sertraline in depressed older adults. Details of the study procedures have been previously reported elsewhere (Sneed *et al.*, 2011). Briefly, patients were recruited by radio and newspaper advertisements and/or through referral from other physicians. Inclusion criteria were (i) age ≥ 45; (ii) unipolar depression, single or recurrent, non-psychotic, by DSM-IV criteria; (iii) HRSD ≥ 16 at the initial visit and at the end of 1 week of placebo; (iv) Mini-Mental State Examination (MMSE) score ≥ 24; and (v) willing and able to give informed consent. Exclusion criteria were (i) current or history of obsessive–compulsive disorder, psychotic disorder, or substance dependence within the past year (other than nicotine) by DSM-IV criteria; (ii) judged to be a current suicide risk or serious suicide attempt within the past year; (iii) patients status post myocardial infarction, coronary artery bypass, or angioplasty, or with a positive history of angina or positive stress test; (iv) QRS interval greater than 0.12 sec or QTc interval ≥ 46 msec; (v) treatment with coumadin, heparin or type 1 antiarrhythmic medications; (vi) diagnosis

of narrow angle glaucoma; (vii) stroke, epilepsy or Parkinson's disease; (viii) acute, severe or unstable medical condition; (ix) positive urine toxicology screen for drugs of abuse including amphetamine, barbiturates, cocaine, marijuana, methadone, methaqualone, opioids, and phencyclidine; and (x) treatment in the current episode of depression with either nortriptyline with a plasma level between 50 and 150 ng/mL, desipramine or imipramine with a plasma level of 250 ng/mL or greater, paroxetine 40 mg, fluoxetine 40 mg, or sertraline 200 mg for at least 4 weeks.

If the patient met inclusion criteria and signed informed consent, a physical examination, electrocardiogram, complete blood count, chemistries, electrolytes, and thyroid panel were performed. The assessments performed at baseline included the HRSD, the Montgomery–Åsberg depression rating scale, the Beck Depression Inventory (BDI-II), the Cumulative Rating Scale for Geriatrics (CIRS-G), the MMSE, the Medical Outcomes Study 36-item short-form health survey, and the CGI of severity and improvement.

Neuropsychological test battery

The test battery was designed to assess a number of cognitive functions pertinent to aging and major depression including general cognitive functioning, psychomotor speed, attention, memory, and executive functioning. The tests included the Folstein MMSE (Folstein *et al.*, 1975) to estimate global cognitive functioning, the Purdue Pegboard (both hands) (Tiffin and Asher, 1948) as a measure of psychomotor speed, the 4-digits fast condition of the Continuous Performance Test–Identical Pairs (Beck *et al.*, 1956) and Trail Making Test A (TMT A) (Reitan, 1955) to assess attention, the Stroop Color/Word test (MacLeod, 1991) and Trail Making Test B (TMT B) (Reitan, 1955) to assess the response inhibition and switching components of executive functioning, respectively, and the Buschke Selective Reminding Test (Buschke and Fuld, 1974) as a measure of verbal learning and memory. Two of the tests (Continuous Performance Test and Stroop Color/Word test) were presented on a Macintosh laptop computer and were written in the PsyScope programming language (Cohen *et al.*, 1993), whereas the other five tests (MMSE, Selective Reminding Test, TMT A and B, and Purdue Pegboard) were paper and pencil.

Magnetic resonance imaging

Imaging procedures, acquisition, and analysis for this study have been previously reported (Sneed *et al.*, 2011). Briefly, MRI scans were carried out on a 1.5 Tesla GE Signa Advantage system. The analyses of lesion volume were based on T_2-weighted axial FLAIR images. Quantification of MRI-hyperintensity volume [total and by regions-of-interest (ROI)] used the MRIcro software (Veltman and Hutton, 2001). The three-step process involves first applying a filter based on an intensity threshold that labels all voxels appearing as hyperintense in red. During the second step, the gross ROI, corresponding to white matter hyperintensity (WMH) in deep cortical areas, is manually traced on a slice-by-slice basis excluding non-WMH areas that are labeled in step 1 (e.g., dermal fat). The distinction between periventricular and deep white matter is made visually following several rules set *a priori* and implemented on each axial slice. WMHs that are contiguous to the lateral ventricles and extend to the deep white matter are classified as periventricular. If there is at least one pixel that separates hyperintense pixels between periventricular and deep areas so that there are two distinct contiguous groups, they are classified separately. During the third step, new images reflecting the intersection of voxels labeled in step 2 with the voxels labeled in step 1 are generated giving total WMH volumes for deep cortical regions. MRIcro provides volumes for the ROI in cm^3, on the basis of the number of labeled voxels and voxel dimensions.

Classification of vascular depression

We used the highest quartile of the distribution of WMH volume scores to quantitatively define VD, which is consistent with recent publications using this method (Gunning-Dixon *et al.*, 2010; Sneed *et al.*, 2011). Qualitative assessment of the severity of hyperintensities used the Fazekas' modified Coffey rating scale (Coffey *et al.*, 1990). WMHs that were disconnected from the ventricular lining were scored as 0 (absent), 1 (punctate foci), 2 (beginning confluence of foci), and 3 (large confluent areas). Patients were identified as having MRI-defined VD on the basis of a DWMH score of 2 or more, which is an empirically-based definition arrived at in a previous report (Sneed *et al.*, 2008a).

Statistical analyses

Using both definitions of VD, we used *t*-tests, w^2 tests of independence, and Fisher's exact tests to test for differences in the clinical profile of patients with and without MRI-defined VD. This included baseline demographic variables as well as clinical variables such

as depression rating scale score and neuropsychological test performance. These analyses were evaluated for statistical significance at the traditional 5% level. To assess diagnostic consistency across the two classification methods, we calculated Cohen's kappa (a chance corrected test of agreement) and McNemar's test (a test used to assess marginal homogeneity) with the use of an exact binomial distribution to account for small sample size. All analyses were conducted using Stata 12 software (StataCorp, 2005).

Results

Quantitative classification of magnetic resonance imaging-defined vascular depression

Magnetic resonance imaging data were available for 38 patients. Of these patients, 10 were classified as having MRI-defined VD based on the highest quartile of the distribution of DWMH volume. Table 1 provides an overview of clinical and demographic characteristics. Patients with MRI-defined VD were significantly older and more likely to be female than patients with non-VD; in fact, 9 out of 10 patients classified as having MRI-defined VD were female. Furthermore, patients with MRI-defined VD demonstrated significantly more psychomotor retardation (as measured by item 8 on the HRSD and performance on the Purdue Pegboard), and significantly worse performance on the interference component of the Stroop Color/Word test (a neuropsychological measure of executive function) than patients with non-VD.

Qualitative classification of magnetic resonance imaging-defined vascular depression

Of the 38 patients, 14 were identified as having MRI-defined VD based on a DWMH score of 2 or higher on the Fazekas' modified Coffey rating scale. Clinical and demographic characteristics are presented in Table 1. Patients with MRI-defined VD were significantly older than patients with non-VD. Patients with MRI-defined VD were also more likely to be female; only 1 patient classified as having MRI-defined VD was male. Patients with MRI-defined VD scored higher on the CIRS-G than patients with non-VD. Furthermore, patients with MRI-defined VD demonstrated significantly more psychomotor retardation on the Purdue Pegboard, and significantly worse performance on the interference component of the Stroop Color/Word test than patients with non-VD.

Assessment of diagnostic criteria

To assess the correspondence between the two diagnostic definitions, we calculated kappa and conducted a McNemar's test. Kappa was estimated to be 0.52, indicating a fair to good agreement beyond chance (Fleiss *et al.*, 2003). McNemar's test revealed that the two marginal probabilities for each outcome are not significantly different ($w^2 = 2$, $df = 1$, $p = 0.16$), which indicates that the likelihood of receiving a VD diagnosis is equivalent across the two definitions.

Post-hoc analysis

Neuropsychological test scores often co-vary with demographic variables such as age, gender, and education. In order to explore the effect of these variables on the relationship between VD status and neuropsychological functioning, we conducted ordinary least-squares (OLS) regression analyses using centered covariates (Table 2). In addition, we calculated effect sizes to determine whether the inclusion of these variables changed the findings substantively or simply reduced the power of the statistical tests due to addition of additional covariates to the model. The relationship between the Purdue Pegboard and VD status was substantively changed after adjusting for age, gender, and education. In addition to no longer being statistically significant, the effect size characterizing the strength of the relationship between the Purdue pegboard and VD status (using either classification procedure) was diminished from large to medium. As for the relationship between performance on the Stroop Color/Word Test and VD status (using either classification procedure), the statistical tests did not reach significance; however, the effect size characterizing the relationship remained large indicating that adjusting for age, gender, and education did not substantively alter the relationship between Stroop performance and VD status.

Discussion

This is the first study to examine the clinical characteristics of MRI-defined VD by comparing two different classification approaches. The findings show that patients with MRI-defined VD based on DWMH burden have a distinct clinical and neuropsychological profile. This profile was largely consistent across different methods for assessing DWMH burden. Compared with patients with non-VD, patients with MRI-defined VD are older and more likely to be female. These patients have a higher CIRS-G score,

Table 1 Comparison of demographic, clinical, and neuropsychological variables between patients classified as having MRI-defined VD using quantitative and qualitative methods

	Quantitative[a]			Qualitative[b]		
	Non-VD (n=28)	VD (n=10)	Analysis	Non-VD (n=24)	VD (n=14)	Analysis
	M (SD)	M (SD)		M (SD)	M (SD)	
Demographic						
Age	64.2 (6.3)	71.1 (8.5)	t(36)=□2.7, p=0.01	63.6 (5.5)	70.2 (8.8)	t(36)=□2.9, p=0.007
Sex (% female)	54	90	p=0.04, Fisher's exact test	46	93	p=0.004, Fisher's exact test
Education	15.5 (3.0)	16.3 (2.9)	t(30)=□0.7, p=0.52	15.5 (3.1)	15.9 (2.9)	t(30)=□0.4, p=0.68
Clinical						
Baseline HDRS	23.6 (5.1)	27.1 (8.2)	t(36)=□1.6, p=0.12	23.8 (5.5)	25.6 (7.1)	t(36)=□0.9, p=0.4
Age at onset	42.6 (21.6)	57.5 (22.2)	t(36)=□1.9, p=0.07	41.7 (20.1)	54.7 (24.7)	t(36)=□1.8, p=0.09
Family history of psychiatric illness (%)	44	22	p=0.23, Fisher's exact test	43	31	p=0.37, Fisher's exact test
Recurrent MDD (%)	59	44	p=0.35, Fisher's exact test	59	50	p=0.42, Fisher's exact test
CIRS-G	3.1 (1.9)	3.6 (1.7)	t(29)=□0.7, p=0.48	2.7 (1.8)	4.1 (1.6)	t(29)=□2.4, p=0.03
CGI-severity	4.1 (1.8)	4.4 (0.8)	t(34)=□0.7, p=0.50	4.1 (1.2)	4.6 (1.0)	t(34)=□1.14, p=0.26
Feelings of Guilt (HRSD item 2)	1	1	w^2(3)=5.0, p=0.18	1	1	w(3)=3.0, p=0.39
Anhedonia (HRSD item 7)	3	3	w^2(1)=2.1, p=0.15	3	3	w(1)=0.5, p=0.47
Psychomotor retardation (HRSD item 8)	0	2	w^2(2)=9.0, p=0.01	0	1	w(2)=2.0, p=0.38
Lassitude (MADRS item 7)	3.4 (1.0)	3.2 (1.2)	t(33)=□0.6, p=0.55	3.3 (1.1)	3.4 (1.0)	t(33)=□0.2, p=0.86
Neuropsychological						
MMSE	27.2 (3.1)	28.1 (1.9)	t(31)=□0.8, p=0.46	28.0 (2.4)	26.4 (3.4)	t(31)=1.6, p=0.12
Buschke SRT	109 (15.8)	101.6 (23.8)	t(30)=1.0, p=0.32	109.4 (16.2)	102.2 (21.5)	t(30)=1.1, p=0.30
Trails A	45.90 (17.0)	58.9 (23.2)	t(31)=□1.7, p=0.10	46.0 (18.8)	55.1 (19.3)	t(31)=□1.3, p=0.21
Trails B	109.7 (56.2)	151.4 (82.7)	t(31)=□1.6, p=0.11	108.3 (53.0)	142.8 (81.5)	t(31)=□1.5, p=0.15
Stroop color/word test	0.4 (0.3)	0.8 (0.5)	t(25)=□2.16, p=0.04	0.4 (0.2)	0.8 (0.5)	t(25)=□2.7, p=0.01
Purdue Pegboard (both hands)	10.9 (2.4)	8.75 (1.9)	t(31)=2.4, p=0.03	11.1 (2.5)	9.0 (1.7)	t(31)=2.5, p=0.02
Continuous performance test (reaction time)	584.3 (80.9)	627.7 (116.7)	t(22)=□0.9, p=0.37	587.7 (86.6)	603.2 (92.8)	t(22)=0.4, p=0.71

[a]Highest quartile of the DWMH volume distribution.

[b]DWMH of two or higher on the Fazekas' modified Coffey rating scale. HDRS, Hamilton Rating Scale for Depression; MDD, major depressive disorder; CIRS-G, Cumulative Illness Rating Scale-Geriatric; CGI, Clinical Global Impression; MADRS, Montgomery–Åsberg Depression Rating Scale; MMSE, Mini-Mental State Examination; SRT, Selective Recall Test; DWMH, deep white matter hyperintensity.

Table 2 Comparison of unadjusted and adjusted[a] effect sizes using qualitative and quantitative approaches to the classification of VD

			Unadjusted				Adjusted[a]		
		n	M (SD)	M_D	Test	Cohen's d	M_D	Test	Cohen's d
Qualitative classification									
Stroop color/word	Non-VD	21	0.4 (0.3)	0.4	$t(25)=2.16$, $p=0.04$	1.19	0.3	$t(25)=1.31$, $p=0.21$	0.9
	VD	6	0.8 (0.5)						
Purdue Pegboard	Non-VD	25	10.9 (2.4)	2.1	$t(31)=2.35$, $p=0.03$	0.94	1.4	$t(25)=1.16$, $p=0.26$	0.6
	VD	8	8.8 (1.9)						
Quantitative classification									
Stroop color/word	Non-VD	19	0.4 (0.2)	0.4	$t(25)=2.71$, $p=0.01$	1.32	0.5	$t(25)=1.65$, $p=0.12$	1.5
	VD	8	0.8 (0.5)						
Purdue Pegboard	Non-VD	22	11.1 (2.5)	2.1	$t(31)=2.53$, $p=0.02$	0.96	1.5	$t(31)=1.32$, $p=0.20$	0.7
	VD	11	9.0 (1.7)						

[a]Adjusted for age, gender, and education

more severe psychomotor retardation (indicated by both higher ratings on the psychomotor retardation item of the HRSD and poorer performance on the Purdue Pegboard), and more impairment on the Stroop Color/Word test (a measure of the response inhibition component of executive functioning). Taken together with previous research establishing the internal validity of MRI-defined VD (Sneed *et al.*, 2008b), these findings support the notion that MRI-defined VD represents a unique and valid subtype of late-life depression that can be accurately identified based on the presence of DWMH burden.

Consistent with our hypothesis, patients with MRI-defined VD are older than patients with non-VD. Indeed, the prevalence cerebrovascular disease increases with age (Bettmann *et al.*, 1998; American Heart Association, 2004); and as a result, the likelihood of having MRI-defined VD also increases with age. Our results further indicate that patients with MRI-defined VD are more likely to be female. Women have been shown to be more vulnerable to cerebrovascular disease than men. This is related to women's greater life expectancy and the higher rates of cerebrovascular disease with increasing age (American Heart Association, 2004). As can be expected, the results of the present study indicate that women are more likely to develop co-occurring MRI-defined VD. Age also increases vulnerability to illnesses other than cerebrovascular disease (Freid *et al.*, 2012). As such, it is likely that older age is associated not only with a higher probability of meeting criteria for MRI-defined VD, but also with an increased number of comorbidities. Indeed, patients classified as having MRI-defined VD score higher on the CIRS-G (a measure of the presence and severity of different medical illnesses) than patients with non-VD.

Our findings confirm that executive dysfunction is a clinical characteristic of patients with MRI-defined VD. Although the association between executive dysfunction and VD is complex, executive dysfunction has frequently been associated with WMHs in late-life depression (Aizenstein *et al.*, 2002; Lockwood *et al.*, 2002; Elderkin-Thompson *et al.*, 2003). In the current study, VD diagnosis was associated with impairment on the Stroop Color/Word test, but not on the Trail Making Test B. The presence of an association between some, but not all, measures of executive functioning and MRI-defined VD is not surprising (Pimontel *et al.*, 2012). Executive functions are complex mental operations that depend on the integration of several more basic cognitive processes (Gunning-Dixon and Raz, 2003). Because different measures of executive function recruit different cognitive abilities (Lezak *et al.*, 2004), impairment on one measure

may not be predictive of impairment on another (Burgess *et al.*, 1998). As such, MRI-defined VD appears to be associated with performance on the response inhibition component of the Stroop Color and Word test, but not on the Trail Making Test B, which measures a variety of executive function processes including cognitive flexibility and working memory.

Taken together with the previous reports (Krishnan *et al.*, 2004), our findings indicate that psychomotor retardation (measured in two distinct ways) is also a clinical feature of MRI-defined VD. However, after controlling for demographic variables, the difference between the performance of patients with and without MRI-defined VD on the Purdue Pegboard (a neuropsychological measure of psychomotor retardation) was no longer significant. The high correlation between performance on the Purdue Pegboard and age may explain these results. As previously discussed, older age is associated with an increased probability of having MRI-defined VD. Additionally, older age is also associated with psychomotor retardation. Therefore, it is likely that patients with MRI-defined VD will have concomitant psychomotor retardation.

The co-occurrence of executive dysfunction and psychomotor retardation in patients with MRI-defined VD raises a critical question about what the two neuropsychological functions have in common (Pimontel *et al.*, 2012). Executive functions depend on the integration of several cognitive processes, including processing speed (Lezak *et al.*, 2004). One possibility, therefore, is that processing speed accounts for the association between executive dysfunction and VD (Story *et al.*, 2008). A decrease in processing speed may disrupt executive processes when relevant operations cannot be completed within the necessary timeframe (Salthouse, 1996). Several studies have shown that processing speed mediates performance on executive functioning tasks in depressed older adults (Degl'Innocenti *et al.*, 1998; Nebes *et al.*, 2000; Butters *et al.*, 2004). However, other studies have shown that executive dysfunction adversely impacts antidepressant treatment response independent of speed of processing in late-life depression (Sneed *et al.*, 2007; Sneed *et al.*, 2008a). Further research is necessary to determine the nature of the relationship between processing speed and executive dysfunction in VD.

According to the psychometric view of psychiatric diagnosis (Skinner, 1981; Sneed *et al.*, 2006; Sneed *et al.*, 2008b), the VD subtype meets criteria for a valid diagnostic entity. It has a coherent theory (Alexopoulos *et al.*, 1997a; Steffens and Krishnan, 1998), the proposed features identify a unique diagnostic subgroup (Sneed *et al.*, 2008b), and executive dysfunction and psychomotor retardation are important clinical characteristics. The course of illness tends to be poor with low response rates to antidepressant medication (Gunning-Dixon *et al.*, 2010; Sneed *et al.*, 2011), frequent recurrence of depression (Alexopoulos *et al.*, 2000), progression of lesion burden (Taylor *et al.*, 2003), and conversion to dementia (Steffens *et al.*, 2003; Barnes *et al.*, 2006).

Limitations

This study was limited in part because of its small sample size. Although we hypothesized *a priori* the direction of differences between VD and non-VD patients, we would have liked to include the group of significant predictors in a controlled analysis to adjust for covariation among these variables. However, we were unable to estimate the parameters of a logistic regression model that included all relevant predictors because of both multicollinearity and the small sample size included in this study. Another limitation was that the sample was predominantly white. This limitation is significant because MRI-defined VD may be overrepresented among African-Americans; this subgroup has higher rates of cardiovascular disease risk factors (Thom *et al.*, 2006), stroke (American Heart Association, 2004), and vascular dementia (American Heart Association, 2004) compared to Caucasians.

Conclusion

Based on the accumulation of evidence over the past two decades, MRI-defined VD appears to be a valid diagnostic subtype of late-life depression. As a result, the field now faces several critical issues. The first is to determine what constitutes significant lesion load and/or executive functioning and whether knowledge of both is needed in order to make treatment recommendations. A clear understanding of these prognostic indicators is critical to developing an evidence-based treatment plan. The second issue is to assess the response rate to antidepressant medication for patients with VD. For example, if patients with VD respond on average at 10% to antidepressant medication, then it is imperative that we actively seek alternative forms of treatment; however, if the average response rate is 40%, then one would still be inclined to use antidepressant medications as a first line treatment. The clinical characteristics we have described in this paper will allow for a more accurate identification of patients with MRI-defined VD, which in turn will allow for more effective treatment, limiting progression of the illness at an early stage.

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Key points

- Several diagnostic criteria have been proposed for defining Vascular Depression (VD) making it difficult to compare findings across studies.
- Patients identified as having VD using both a qualitative and quantitative definition have a characteristic clinical and neuropsychological profile that is distinct from that of patients with non-vascular depression.
- Qualitative and quantitative methods for defining VD identify a mostly similar subgroup of patients
- These findings support VD as a unique and valid subtype of late-life depression.

Conflict of Interest

None declared.

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