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Neuropsychological correlates of magnetic resonance imaging-defined subcortical ischemic depression

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Abstract

Objective—The goal of the current study was to examine the neuropsychological profile of magnetic resonance imaging (MRI)-defined subcortical ischemic depression (SID).

Methods—Clinically depressed older adults with MRI-defined SID (n = 70) and depressed elders without SID (n = 75) were compared on neuropsychological performance, depression symptoms and medical burden.

Results—Group comparisons revealed that the SID was associated with worse performance on all neuropsychological measures, but also with greater age, higher cardiac illness burden, and greater deficits in the depression symptoms of self-initiation and concentration. In multivariate regression models, auditory working memory and nonverbal memory remained worse among the SID group after controlling for contributions of age, cardiovascular risk, and depression symptoms.

Conclusions—Although auditory working memory span and nonverbal memory appear to be specifically associated with the ischemic pathology that defines SID, the typical individual with SID is also likely to have a broader profile of neuropsychological deficits than those without SID because they are typically older and have profiles of depression symptoms that predispose them to compromised neurocognitive performance.

Keywords

geriatric depression; vascular depression; neuropsychology; cognition

Key points

- MRI-defined subcortical ischemic depression is associated with a specific profile of neurocognitive and behavioral deficits that appears to reflect the underlying cerebrovascular pathology
- Vascular depression likely involves multiple reciprocal influences of cerebrovascular pathology and depression symptoms that adversely effect both cognition and functional outcomes (Steffens *et al.*, 2002a).

INTRODUCTION

Research on geriatric depression has highlighted important relationships among cerebrovascular pathology, neurocognitive deficits, and depression symptoms. Magnetic resonance imaging (MRI) studies demonstrate associations between deep-white-matter hyperintensities and deficits in executive functions and memory among depressed elders, a finding that was not seen among elderly depressed lacking in DWMH, nor among normal controls with or without DWHM (Kramer-Ginsberg *et al.*, 1999). Subcortical hyperintense lesions are associated with slowed information processing and deficits in attention and executive functions (Gunning-Dixon and Raz, 2000), which may become more pronounced after a “threshold” volume of white matter lesion area is reached (Boone *et al.*, 1992). Subcortical ischemic lesions are also more common among older adults diagnosed with depression than those without depression (Krishnan *et al.*, 1993; Kumar *et al.*, 2000). These studies suggest that ischemic pathology is important to characterize because it may result in acquired dysfunction in both mood and cognition.

Krishnan and colleagues proposed a definition of vascular depression based on MRI evidence of ischemic pathology (Krishnan *et al.*, 1997; Steffens and Krishnan, 1998; Krishnan *et al.*, 2004). This definition of subcortical ischemic depression (SID) characterized approximately 50% of individuals from a clinical outpatient sample, and the authors found that individuals with MRI-defined SID were characterized by greater age, more prominent lassitude, and more frequent history of hypertension relative to depressed individuals without SID. The authors concluded that SID may help characterize a specific subtype of vascular late-life depression, and that this definition should be further defined with respect to its clinical characteristics and risk factors (Taylor *et al.*, 2006). Given the interrelationships among depression, vascular disease, and neurocognitive function, it is important to examine whether this MRI-defined diagnosis of SID has a characteristic neuropsychological profile.

The objective of this study was to compare neuropsychological performance among depressed older adults with SID to depressed elders without SID. We expected worse neuropsychological performance in SID overall, with the largest decrements on tests of information processing speed and executive functions. We planned to covary for factors associated with SID that may also influence neurocognitive function, including age, medical burden, and depression severity. In addition, we planned to examine whether specific cardiovascular and depression profiles may also be associated with neuropsychological performance in SID. Vascular risk factors have been associated with clinical definitions of vascular depression (Alexopoulos *et al.*, 1997), and MRI-defined SID was specifically associated hypertension history (Krishnan *et al.*, 2004). Research also found that individuals with SID have deficits in self-initiation (lassitude) relative to individuals without SID (Krishnan *et al.*, 2004). We planned to examine vascular risk factors and depression symptoms and covary for those elements other than ischemic pathology that may influence neurocognitive performance in SID.

METHODS

Participants

Participants were 145 depressed individuals enrolled in a clinical treatment study. Participants met DSM-IV criteria for major depression and were at least 60 years old at enrollment. Exclusion criteria were: 1) another major psychiatric illness; 2) alcohol or drug abuse/dependence; 3) primary neurological illness, including dementia; and 4) non-psychotropic medications, medical illness, or physical disability clinically determined to affect cognitive function. Written informed consent was obtained from participants after a

complete description of the study. This study was approved by the Institutional Review Board at Duke University Medical Center.

Procedure and Measures

Clinical Assessment—Participants received a full examination by a geriatric psychiatrist and completed standardized clinical assessments to rule out exclusionary Axis I diagnoses and further characterize depression. Portions of the National Institute of Mental Health Diagnostic Interview Schedule (DIS; Robins *et al.*, 1981) were used to rule out other Axis I diagnoses. The Montgomery-Asberg Depression Rating Scale (MADRS (Montgomery and Asberg, 1979) was used to characterize depression symptoms and severity in the current study. The MADRS is a 10-item scale of depression severity based on self report and clinical observation, and was completed by the treating psychiatrist at entry to the study.

Treatment protocol—Participants were treated by a geriatric psychiatrist based on the Duke STAGED approach (Steffens *et al.*, 2002b), which follows a standardized naturalistic treatment algorithm. At the time of testing, 72 participants were taking antidepressants, including sertraline (n = 15), bupropion (n = 13), fluoxetine (n = 9), mirtazepine (n = 8), nortriptyline (n = 8), paroxetine (n = 5), nefazodone (n = 4), trazodone (n = 2), escitalopram (n = 1), and phenelzine (n = 1). Other participants were taking methylphenidate (n = 4) and St. John's Wort (n = 1); in addition, some were taking benzodiazepines (n = 28), buspirone (n = 1), gabapentin (n = 4), and narcotic-containing pain medications (n = 4).

Dementia screening—Exclusion for dementia was based on psychiatrist assessment of suspected dementia at baseline, including clinical examination, medical records, and mental status examination. Individuals who performed below a cut-off value of 25 on their baseline Mini-Mental State Examination (MMSE; Folstein *et al.*, 2001) were re-assessed following 12-weeks of pharmacological treatment, and individuals remaining below a score of 25 were excluded.

MR Imaging: Hyperintense Lesion Severity Measurements—Brain MRI occurred at study entry. Two sets of images were utilized for lesion ratings. Set 1: axial, multi-section, T1-weighted pulse sequence (TRs500 ms, TE15 ms), 256 = 192 data acquisition matrix, 5-mm section thickness, 20-cm FOV, 1 excitation per phase encoding increment (1 Nex), and a 32 kHz ("16 kHz) full imaging bandwidth. Set 2: long TR (2500 ms), double-echo (TEs30 and 80 ms) spin-echo data acquisition sequence with same FOV, section thickness, bandwidth and spacing as Set 1; 256 = 192 data acquisition matrix, and 1 Nex. Images were obtained in two separate acquisitions with a 5-mm gap between sections for each acquisition. The second acquisition was offset 5 mm from the first to obtain a dataset of contiguous sections. Complete description appears elsewhere (Payne *et al.*, 2002).

The methodology defining SID was based on the Coffey classification system (Coffey and Figiel, 1991), as originally described by Krishnan *et al.* (Krishnan *et al.*, 2004). This approach allows weighting of both size and quantity of lesions when assigning a severity rating. This system uses predefined visual standards (Fazekas *et al.*, 1988) to grade lesion severity. Deep white matter hyperintense (DWMH) lesions were scored as 0 (absent), 1 (punctate foci), 2 (beginning confluence of foci), or 3 (large confluent areas). Subcortical gray matter hyperintense (SCH) lesions were scored as 0 (absent), 1 (punctate), 2 (multipunctate), or 3 (diffuse). Scores reflected the most severe lesion visualized on the entire MRI series and were determined by consensus opinion between two investigators blinded to participant status. The intraclass correlation coefficient (ICC) for DWMH was .85, and the ICC for SCH was .80 (Krishnan *et al.*, 1997). SID was defined as a Coffey

classification score of 2 or 3 for DWMH or a classification score of 3 for SCH (Krishnan *et al.*, 2004).

Neuropsychological Assessment—Several tests from the baseline neuropsychological assessment were selected to represent specific domains of performance in this study. General cognitive status was assessed with the Mini-Mental State Examination (Folstein *et al.*, 2001). Auditory working memory was by Digit Span Forward and Backward trials (Wechsler, 1987a). Information processing speed/executive functions were assessed by the Symbol-Digit Modalities Test (SDMT, Smith, 1982) and Parts A and B of the Trail Making Test (Reitan, 1992). Verbal memory was assessed with immediate (Logical Memory I) and delayed (Logical Memory II) recall from the Wechsler Memory Scales-Revised (WMS-R; Wechsler, 1987b). Nonverbal immediate memory was assessed using the Benton Visual Retention Test (BVRT; Benton, 1974). Verbal fluency was assessed with a one-minute Animal Naming test.

Medical Burden—Medical burden was assessed with the Cumulative Illness Rating Scale (Conwell *et al.*, 1993), which rates 12 organ systems on a 5-point scale, ranging from 0 (No problem or impairment) to 4 (Extremely severe). In addition, we specifically examined items related to two systems: 1) cardiac (heart only) and 2) vascular (blood, blood vessels and cells, marrow, spleen, lymphatics). Ratings were obtained by treating psychiatrists.

Statistical Methods

Participants were dichotomized as SID or non-SID. Group differences on demographics and neuropsychological performance were examined using pooled-variance t-tests for equal variance and Satterthwaite t-tests for unequal variance. Sex and race were examined using a chi-square test. Neuropsychological measures that were significantly different between groups were included as dependent variables in separate regression models, in which they were each regressed on a dichotomous variable denoting SID status (SID = 1), along with covariates of age, medical burden, and depression symptoms. All independent variables were entered into the models simultaneously.

RESULTS

Means and standard errors of demographic and clinical variables are shown in Table 1. Individuals with SID were older and had greater cardiac burden, but did not differ in education, sex, race, vascular system burden, or overall medical burden. Individuals with SID had higher depression scores overall. Among individual MADRS items, individuals with SID had greater difficulty with self-initiation (lassitude) and concentration, but did not differ on other individual depression symptoms.

Means and standard errors of neuropsychological measures are presented in Table 2, stratified by SID status. Individuals with SID performed worse on all 10 neurocognitive measures.

Multivariate models regressed neuropsychological performances on SID status while simultaneously controlling for age, depression, and medical burden. SID was associated with worse performance on 4 measures: Digit Span Forward ($b = -1.28, t = 2.76, p < 0.01$), Digit Span Backward ($b = -0.96, t = 2.16, p < 0.05$), BVRT ($b = -0.77, t = 2.17, p < 0.05$), and Trail Making B ($b = 28.01, t = -2.01, p < 0.05$). Among other variables in the models, age predicted worse neuropsychological performance for 8/10 measures (all but Digit Span Forward and Digit Span Backward) and depression severity predicted worse neuropsychological performance for 7/10 measures (all but Digit Span Forward, Digit Span

Backward, and BVRT). Medical burden did not predict neuropsychological performance in these models.

Next, we examined the models substituting cardiovascular burden (CIRS Heart item) for overall medical burden, and substituting the sum of the Lassitude and Concentration items of the MADRS for overall depression severity. In these models covarying for specific depression symptoms and specific cardiovascular burden along with age, SID was still associated with lower scores on Digit Span Forward and BVRT (Table 3). Among other variables in the models, age was associated with worse neuropsychological performance on 8/10 measures (all but Digit Span Forward and Digit Span Backward) and the Lassitude/Concentration items were associated with worse neuropsychological performance on 2/10 measures (MMSE and Trail Making B). The CIRS Heart item did not predict neuropsychological performance in these models.

DISCUSSION

The current study sought to characterize the neuropsychological profile associated with a proposed MRI-based definition of subcortical ischemic depression (SID). We found that individuals with SID had worse neuropsychological performance across a broad range of tests than depressed individuals without SID. Four tests- Digit Span Forward, Digit Span Backward, Benton Visual Retention, and Trail Making B- remained significantly worse in the SID group after controlling for the influences of age, depression severity, and medical burden on neuropsychological performance. When we changed the models to control for the influence of clinical characteristics that specifically differed between the SID and non-SID groups, we found that Digit Span Forward and Benton Visual Retention were still lower in association with SID when lassitude and concentration deficits were substituted for overall depression severity and cardiovascular burden was substituted for overall medical burden. Lower neuropsychological performance on these two tests appears to reflect an adverse influence of underlying ischemic pathology beyond the effects of other clinical characteristics of SID.

This study adds to existing research on depression by expanding the clinical characterization of MRI-defined vascular depression. We found that while depressed individuals with SID had worse neuropsychological performance as a group than depressed individuals without SID, the source of the neuropsychological differences includes not only ischemic pathology, but also greater age and depression severity, specifically lassitude and concentration complaints. In fact, higher age and greater depression severity of individuals with depression were the two most robust predictors of neuropsychological deficits; however, we also found that neither age nor depression were associated with performance on Digit Span forward; rather, differences were due to the ischemic pathology that defined the SID group. We also found initiation deficits (lassitude) and concentration deficits to be more prominent among individuals with SID, and that these symptoms were associated with worse neuropsychological performance on some tests. Our findings highlight that SID has multiple clinical characteristics that contribute to neuropsychological deficits in addition to the underlying ischemic pathology.

The neuropsychological findings in this elderly depressed sample are consistent with neuroimaging findings in middle-aged and older adults with cerebrovascular pathology. A study of middle-aged hypertensives found deficits on Digit Span Forward to be associated with more white matter lesions (Sierra *et al.*, 2004). Similarly, a study of healthy adults aged 45 and over found that Digit Span Forward was lower among the group of individuals with the highest volume of white matter lesions, which was approximately 6% of the sample with a lesion volume greater than 10 cm². Other measures, including verbal fluency and verbal

memory, were not associated with white matter lesions (Boone *et al.*, 1992). An MRI study including the BVRT found that greater prevalence of T2 high signal intensity lesions was associated with lower BVRT performance (Kasahara *et al.*, 1995) among healthy elderly.

Although we present an MRI-based definition of vascular depression in this study, there are other definitions of this condition. Clinically defined vascular depression (Alexopoulos *et al.*, 1997) is characterized by the presence of vascular risk factors and neuropsychological test performances consistent with subcortical dysfunction, specifically in the domains of attention and executive functions. Another conceptualization of vascular pathology in depression comes from post-mortem evaluations that found more white matter ischemia in the DLPFC of older depressed individuals than non-depressed comparison individuals, which was characterized as supporting the vascular depression hypothesis (Thomas *et al.*, 2003). The current study supports the idea that neurocognitive deficits in auditory working memory and nonverbal memory are present in conjunction with ischemic pathology and depression. The MRI-based definition of vascular depression posed in our study appears complementary to clinical and neuropathological characterizations posed by other researchers.

One clinical implication of this study is that neuropsychological assessment may help identify individuals with a combination of neurocognitive deficits and cerebrovascular pathology that places them at greater risk for adverse outcomes, including greater treatment resistance (Simpson *et al.*, 1998; Potter *et al.*, 2004) and more functional disability (Kiosses *et al.*, 2001; Steffens *et al.*, 2002a). As a group, depressed individuals with SID performed worse than non-SID individuals on the MMSE and all nine neuropsychological measures. It is important to note that even though Digit Span Forward and BVRT were the only neuropsychological measures with unique contributions from the ischemic differences between depressed groups after controlling for age, lassitude/concentration deficits, and cardiovascular burden, the presence of other clinical factors may contribute to broader neuropsychological deficits in the typical patient with SID, because he or she is likely to be older, to have more difficulty with self-initiated behavior (lassitude) and concentration, and to have vascular risk factors for ongoing ischemic risk (DeCarli *et al.*, 1995; Brady *et al.*, 2005).

The clinical utility of an MRI-based approach to identifying vascular depression is highlighted by findings that deep white-matter hyperintensities were greater among depressed individuals even when controlling for cerebrovascular risk factors (O'Brien *et al.*, 1996). This finding suggests that relying solely on the presence of vascular risk factors to diagnose vascular depression may lack sensitivity to detect cerebrovascular pathology in the context of depression, and that neuropsychological testing may be a useful adjunct to an MRI-based diagnosis.

One limitation to the current study is that the definition of SID does not account for precise lesion locations. Although lesion localization may be an important factor in clinical presentation and course, the current data also suggest that cerebrovascular pathology in depression can be characterized more broadly. It would be useful to examine in future studies if specific lesion locations account for subtypes of symptom presentation, neurocognition, or clinical outcome within the construct of vascular depression. Greater specificity in the associations among structural and clinical characteristics may lead to more precise neuroimaging-based definitions of vascular depression.

Another potential limitation is that participants were enrolled in a naturalistic treatment program in which some participants were not under pharmacologic treatment and treatment regimens differed among those who were taking antidepressant medications. Some

individuals were also taking benzodiazepines in addition to antidepressants. To assess this further, we examined proportions of individuals on any antidepressant medication by SID status and found no group differences. We also examined proportions of individuals on benzodiazepines by SID status and found no group differences. Although most participants on antidepressant medication were taking an SSRI, it is possible that variation in specific agents or use of benzodiazepines may have resulted in additional error variance in predicting neuropsychological performance; thus, it would be useful to compare the current results to those of no-treatment or single-agent trials.

The current study carries the typical caveats of cross-sectional design. Although this design leaves us unable to answer questions regarding the extent to which vascular ischemia causes depression (Rainer *et al.*, 2006) or affects its course, it does support the view that the combination of depression and cerebrovascular disease in older adults is associated with greater neurocognitive deficit, specific depression symptoms, and the presence of cardiovascular risk factors. To advance the characterization of SID as a diagnostic entity, it will be important to examine clinical and neurocognitive outcomes over time, including the relationship between SID and development of dementia (Steffens *et al.*, 2003b).

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Table 1

Sample characteristics of depressed SID and non-SID groups.

	SID Mean (SE)	Non-SID Mean (SE)	Statistic <i>t</i> or χ^2 (df)
Age	70.96 (0.84)	65.97 (0.62)	<i>t</i> (129) = -4.76 ^{b, c}
Education	13.66 (0.33)	14.33 (0.33)	<i>t</i> (143) = 1.46
% female	67%	65%	χ^2 (1) = 0.05
% Caucasian	48%	51%	χ^2 (1) = 0.53
MADRS	28.07 (0.95)	25.68 (0.73)	<i>t</i> (143) = -2.00 ^a
Concentration	3.00 (0.13)	2.59 (0.13)	<i>t</i> (143) = -2.23 ^a
Lassitude	3.39 (0.14)	2.95 (0.11)	<i>t</i> (143) = -2.49 ^a
CIRS	4.33 (0.37)	3.68 (0.34)	<i>t</i> (143) = -1.31
CIRS Heart	0.88 (0.12)	0.46 (0.08)	<i>t</i> (120) = -2.41 ^{a, c}

MADRS = Montgomery-Asberg Depression Rating Scale; Concentration = MADRS item #6; Lassitude = MADRS item #7; CIRS = Cumulative Illness Rating Scale

^a *p* < .05

^b *p* < .01

^c unequal variance

Table 2

Neuropsychological profile of depressed SID and non-SID.

	SID Mean (SE)	Non-SID Mean (SE)	Statistic <i>t</i> (df)
MMSE	27.53 (0.26)	28.40 (0.21)	<i>t</i> (143) = 2.63 ^b
Digit Span F	7.55 (0.30)	8.87 (0.30)	<i>t</i> (121) = 3.18 ^b
Digit Span B	6.25 (0.26)	7.38 (0.31)	<i>t</i> (121) = 2.77 ^b
SDMT	32.68 (1.41)	39.53 (1.29)	<i>t</i> (139) = 3.59 ^b
Trail Making A	59.07 (4.43)	45.83 (3.43)	<i>t</i> (143) = -2.38 ^a
Trail Making B	171.74 (11.07)	119.89 (8.08)	<i>t</i> (124) = -3.78 ^{b, c}
LM I	20.76 (0.99)	25.07 (0.99)	<i>t</i> (143) = 3.21 ^b
LM II	16.54 (1.10)	21.36 (1.06)	<i>t</i> (143) = 3.16 ^b
BVRT	4.61 (0.26)	5.92 (0.21)	<i>t</i> (141) = 3.91 ^b
Animal Naming	14.61 (0.51)	16.95 (0.61)	<i>t</i> (143) = 2.91 ^b

MMSE = Mini-Mental State Examination; Digit Span F (Forward), B (Backward); SDMT = Symbol-Digit Modalities Test; LM = Logical Memory; BVRT = Benton Visual Retention Test

^a *p* < .05

^b *p* < .01

^c unequal variance

Table 3

Results of Subcortical Ischemic Depression (SID) and covariates in multivariate regression predicting Digit Span Forward and Benton Visual Retention Test performance, simultaneous entry

	b (SE)	t	p
Digit Span F			
SID	-1.304 (0.47)	2.76	<0.01
CIRS Cardio	-0.195 (0.25)	-0.77	ns
MADRS LC	0.097 (0.12)	0.82	ns
Age	-0.003 (0.03)	-0.10	ns
BVRT			
SID	-0.837 (0.37)	2.29	<0.05
CIRS Cardio	-0.189 (0.20)	-0.95	ns
MADRS LC	-0.002 (0.09)	-0.02	ns
Age	-0.079 (0.03)	-3.01	<0.01

SID = 1 (non-SID = 0) in model. Digit Span F (Forward), Benton Visual Retention Test (BVRT), SID = subcortical ischemic depression, CIRS Cardio = Cardiovascular item from Cumulative Illness Rating Scale; MADRS LC = Lassitude and Concentration items from the Montgomery-Asberg Depression Rating Scale; ns = not significant