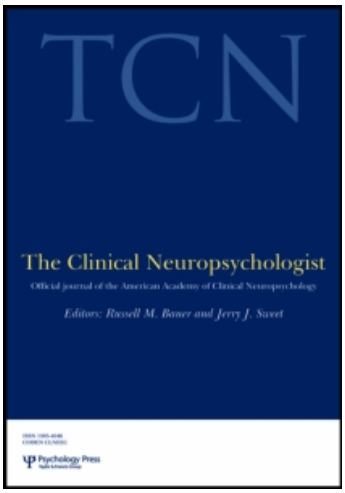

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LEUKOARAIOSIS SEVERITY AND LIST-LEARNING IN DEMENTIA

Catherine C. Price[1], Kelly Davis Garrett[2], Angela L. Jefferson[3], Stephanie Cosentino[4], Jared J. Tanner[1], Dana L. Penney[5], Rodney Swenson[6], Tania Giovannetti[7], Brianne Magouirk Bettcher[7], and David J. Libon[8]

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In patients with dementia, leukoaraiosis (LA) was hypothesized to result in differential patterns of impairment on a verbal serial list-learning test. Using a visual rating scale, 144 dementia patients with ischemic scores <4 were re-categorized as having mild (n = 73), moderate (n = 44), or severe LA (n = 27). Mild LA was predicted to be associated with an amnestic list-learning profile, while severe LA was predicted to be associated with a dysexecutive profile. List-learning performances were standardized to a group of healthy older adults (n = 24). Analyses were conducted on a set of four factors derived from the list-learning paradigm, as well as error scores. Data indicate that LA severity is an important marker for understanding list learning in dementia.

Keywords: Alzheimer's disease; Vascular dementia; Binswanger's disease; Subcortical dementia; Episodic memory; The Philadelphia (repeatable) Verbal Learning Test (PrVLT).

INTRODUCTION

It is well known that on verbal serial list learning tests, patients with pathology in the medial temporal lobes often produce a very shallow and flat learning curve on immediate recall test trials, suffer a rapid rate of forgetting, and perform poorly on delayed recognition testing. They also produce a large number of extra-list intrusion errors on category cued recall test trials (Canolle et al., 2008; Delis et al., 1991). We label this an *amnesic* profile. In contrast, patients with subcortical diseases such as Parkinson's disease (PD) exhibit less forgetting, make fewer intrusion errors, and score relatively better on delayed

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recognition test conditions (Kramer et al., 1988; Massman, Delis, Butters, Levin, & Salmon, 1990). Elements of episodic memory impairment exhibited by these patients may be due, in part, to frontal system dysfunction or executive control deficits, and reflect a source recall problem (Dobbins, Simons, & Schacter, 2004). We label this a *dysexecutive* profile.

The current research investigated the direct effect of MRI-leukoaraiosis (LA; Hachinski, Potter, & Merskey, 1987) on these verbal serial list-learning performances in patients with mild to moderate dementia. Briefly, LA is not a disease but defines areas of hyperintense pixels within the white matter on CT/MRI studies. LA occurs in healthy older adults and in dementia such as Alzheimer's disease and subcortical vascular dementia (sVD; also known as ischemic vascular dementia or small vessel vascular disease). Within these populations, LA is often believed to be a marker of ischemia (see Chui, 2007, for review), although some argue that LA may signal the presence of other pathological processes such as Wallerian degeneration (Leys et al., 1991), amyloid-induced oligodendrocyte toxicity (Xu et al., 2001), and endothelial dysfunction due to genetic variations (Szolnoki, 2007). Clinically, large amounts of LA have been associated with subcortical profiles with slow processing speed and impaired working memory. This suggests that LA may signify frontostriatal pathway disruption (for rationale review, see Libon, Price, Garrett, & Giovannetti, 2004; for review of pathways, see Alexander, DeLong, & Strick, 1986).

Among older adults with dementia, research suggests that neuropsychological profiles differ by LA severity. Patients with little to no LA demonstrate more memory than executive function impairment; patients with moderate LA (estimated to involve approximately one fourth of the white matter) present with equal disruption on memory and executive tests; patients with severe LA (estimated to involve approximately at least half of the white matter) are distinguished by a striking dysexecutive syndrome (Libon et al., 2008; Price, Jefferson, Merino, Heilman, & Libon, 2005). These three LA groups show comparable overall dementia severity (i.e., equal scores on tests such as the Mini Mental State Examination; Folstein, Folstein, & McHugh, 1975). This suggests that differential patterns of impairment on neuropsychological tests reflect discrete dementia syndromes with distinct gray and white matter etiologies rather than a single progressive LA syndrome.

In this study we sought to better understand how LA severity marks verbal serial list-learning performance, for successful list-learning is influenced by both memory and executive systems (Tremont, Halpert, Javorsky, & Stern, 2000). Based on earlier findings, we hypothesized that individuals with mild LA would demonstrate an amnestic pattern. In contrast, severe LA would demonstrate a dysexecutive profile. Moderate LA would demonstrate a mixed profile.

To investigate this general hypothesis we quantified LA in patients with mild to moderate dementia who have a Hachinski ischemic stroke score of less than 4 (Hachinski, Lassen, & Marshall, 1974). We used LA severity as the grouping variable, while ignoring dementia diagnosis (i.e., AD, sVD). This was strategic for two basic reasons. First, the clinical diagnosis of dementia is now even more complex due to accumulating literature demonstrating that, upon autopsy, many brains contain hallmark features of both AD and small vessel vascular pathology.

There are increasing reports of mixed pathology in individuals meeting clinical criteria for AD (Barker et al., 2002) with fewer numbers of so-called "pure" AD patients (White et al., 2005). Comparatively, sVD patients have been shown to have significant cortical and hippocampal atrophy without AD pathology (Fein et al., 2000; Laakso et al., 1996). From a pathological viewpoint, therefore, the line between the two diagnoses has become blurred. Second, despite a number of diagnostic schemes proposed to distinguish sVD from AD, the sensitivity and specificity of these diagnostic schemes is questionable; patients meeting sVD using one diagnostic scheme do not necessarily qualify for sVD diagnosis using a different set of criteria (i.e., the ADDTC and the NINDS-AIREN criteria for the diagnosis of sVD; Cosentino et al., 2004a; Pohjasvaara, Mantyla, Ylikoski, Kaste, & Erkinjuntti, 2000; see Jellinger, 2007 for review). Cosentino et al. (2004a) also found that some patients who met NINCDS-ADRDA criteria for AD also met diagnostic criteria for sVD. Dementia seen in community-dwelling patients may therefore be driven by interactions between gray and white matter changes.

For these reasons our research group has chosen the neuroimaging variable of LA as the independent variable. This has methodological advantages as well. The radiological classifications are performed by examiners who are blind to the patients' clinical presentation or neuropsychological data. Using LA severity, rather than diagnosis, to group patients also circumvents the circularity problem that exists when neuropsychological constructs (which are often core criteria for diagnostic classification) are studied as the dependent variables. Previous research shows that examining dementia by LA severity reveals differential patterns of impairment in grammatical comprehension (Giovannetti et al., 2008), working memory (e.g., Lamar et al., 2007), and visuoconstruction (Cosentino et al., 2006).

For the present study we specifically hypothesized distinct serial list learning patterns and error presentation. We expected LA group differences on immediate, delay, recognition index comparisons and error production (i.e., intrusion characteristics, perseverations). We hypothesized that individuals with mild amounts of LA would produce an *amnesic* pattern (i.e., pronounced forgetting after a delay and failure to benefit from recognition testing). Error analysis would identify this group to produce many extra-list intrusion errors on category cued recall testing, with these more frequent in the English language suggestive of reduced lexical and semantic integrity. We also expect this group to over-endorse recognition foil types, symbolizing failure to benefit from recognition testing. In contrast, the severe LA would produce a *dysexecutive* pattern on a nine-word list-learning test design for dementia (i.e., despite poor performance on free recall testing, these patients would benefit from delayed recognition testing). Additionally, individuals with severe LA would produce minimal intrusions throughout testing, but more perseverations than the other two groups. The severe LA group would also demonstrate susceptibility to recognition test foils that pulled items from the interference test condition. We expected that the moderate LA group will fall in between the mild and severe LA groups and present with features of the amnesic as well as the dysexecutive profiles described above.

METHOD

Participants

A cohort of 144 mild to moderate dementia outpatients was drawn from an outpatient, university-affiliated memory clinic. This group includes an original set of 115 patients reported upon by Libon et al. (2008) and 29 new prospectively recruited patients. A team consisting of a neurologist, neuropsychologist, and social worker diagnosed the presence of dementia based on (1) a decline in activities of daily living (ADLs) and/or instrumental activities of daily living (IADLs; Lawton & Brody, 1969), (2) medical and neurological evaluations including an MRI study of the brain and laboratory studies to assess for reversible causes of dementia, (3) a comprehensive neuropsychological evaluation that included the P(r)VLT, and (4) a social work assessment. A brain MRI was obtained on all dementia patients within 2 weeks of the neuropsychological assessment. Using the criteria of McKhann et al. (1984) and Chui et al. (1992), our sample consisted of 83 patients who met criteria for probable AD (McKhann et al., 1984) and 61 patients who met criteria for the diagnosis of probable/possible ischemic vascular dementia (also known as subcortical vessel vascular dementia, sVD; Chui et al., 1992). As mentioned earlier, however, due to growing evidence of pathology overlap and validity concerns for several sVD diagnostic criteria, we will not base our analyses on these dementia diagnoses. No dementia outpatient presented with an ischemic score < 4 (Hachinski et al., 1974), no patient presented with either a sudden onset of cognitive decline or a stepwise course with respect to their dementing illness, and findings on the neurological examination were non-focal for all patients.

Also included is a new set of community-dwelling non-demented (ND) older adult controls to provide a reference PrVLT for *z*-score calculation. The ND control participants were recruited from independent retirement centers. Neuropsychologists (CP, DL, DP) or supervised trainees screened for physical, mental health, and cognitive difficulties. Cognitive inclusion criteria required a Mini-Mental State Examination ≥ 26 (MMSE; Folstein et al., 1975) and intact daily living (IADLs; Lawton & Brody, 1969). Additionally, each control had a Boston Naming Test age and education corrected T-score ≥ 40 (Heaton, Miller, Taylor, Grant, 2004; Kaplan, Goodglass, & Weintraub, 1983; group raw mean $= 53.13 \pm 6.30$), and performed normally on a test of Clock Drawing (Libon, Malamut, Swenson, Sands, & Cloud, 1996a; e.g., group command executive error mean $= .21 \pm .41$).

Dementia and ND participants were excluded if there was endorsement of current depression via interview and subjective measurement (Geriatric Depression Scale, GDS; Yesavage et al., 1983), history of stroke (excluding evidence of incidental small vessel lacunes on dementia MRIs, which were coded as either present or absent), major medical/CNS disease, seizure disorder, thyroid disease, closed head injury, substance abuse, major depression, or other serious psychiatric disorders. All participants were ambulatory and relatively medically well and stable. Informed written consent was obtained according to Institutional Review Board guidelines and the Declaration of Helsinki.

Brain MRI protocol

A 1.5 Tesla Siemens magnetic scanner was used to obtain brain MRI data on the outpatient dementia participants. Both T1 (TR/TE = 500 ms/15ms) and T2 (TR/TE = 4000 ms/90ms) weighted studies were obtained in order to better discriminate areas with LA from perivascular spaces and lacunes. The severity of white matter alterations was quantified using a visual rating, 40-point scale, Junque Leukoaraiosis Scale (Junque et al., 1990). This scale divides each hemisphere into five areas: frontal centrum semiovale, parietal centrum semiovale, white matter around the frontal horns, white matter around the body of the lateral ventricles, and white matter around the atrium and the occipital horns. The severity of LA in each area was graded from 0 (no visible LA) to 4 (severe LA) and then all area scores were summed (WMA score range = 0–40; 40 = no intact white matter present). LA scores were calculated by a board-certified neuroradiologist who was blind to all clinical information and had established excellent inter-rater reliability for a previous investigation (inter-rater reliability, $r = .98$, $p < .001$; Libon et al., 1998). The Junque LA scale's validity has been based on relations between severe LA scores and poor performance on a wide variety of tests that measure executive control, working memory, and information-processing speed (Lamar et al., 2007; Libon et al., 2004, 2008; Price et al., 2005).

LA group classification (mild, moderate, severe)

LA group division was based on cut-points reported in our prior work demonstrating that specific levels of LA contribute to different neuropsychological profiles in patients with dementia (see Libon et al., 2008; Price et al., 2005). In these earlier studies we calculated the Junque LA scale frequency distribution and subdivided the Junque LA scores into three equal portions (i.e., mild, Junque score = 0–8; moderate Junque = 9–17; severe Junque = 18 and higher). Similar to previous publications (Libon et al., 2008; Price et al., 2005), these cut-points resulted in the following: a *mild LA group* with a Junque LA mean suggesting 10.03% abnormality in the white matter ($n = 73$, Junque mean ± SD = 4.01 ± 2.78), a *moderate LA group* with a Junque LA mean indicating 30.05% abnormality ($n = 44$, mean ± SD = 12.02 ± 2.26); a *severe LA group* with a Junque LA mean indicating 54% abnormality ($n = 27$, mean ± SD = 22.30 ± 4.35).

There were no significant differences in age, education, MMSE, or GDS between the three LA groups (all p values $\geq .06$) or between education and GDS relative to the PrVLT reference control group (all p values $> .11$). The reference control group, used for standardizing the PrVLT factors, was similar in all demographic variables to the LA groups, with the exception of age for the moderate LA group ($p = .003$, control group younger). The reference control group also had higher MMSE scores than the LA groups (all p values $< .001$). There were more females than males in each participant group ($p < .01$). See Table 1 for participant details.

Table 1 Group means, standard deviations, and frequencies for leukoaraiosis (LA) and demographics

	Mild ($n=73$)	Moderate ($n=44$)	Severe ($n=27$)	NC ($n=24$)	p value
LA Junque Score	4.01 ± 2.78	12.02 ± 2.26	22.30 ± 4.35	–	$<.001$
Age	78.52 ± 5.69	80.95 ± 4.98	79.44 ± 4.43	75.63 ± 9.39	*
Education	12.56 ± 2.82	12.16 ± 2.76	11.93 ± 2.13	13.73 ± 2.67	*ns*
MMSE	22.58 ± 3.01	22.36 ± 3.60	21.74 ± 3.13	28.21 ± 1.25	$<.001$
GDS	3.56 ± 2.77	3.68 ± 3.20	4.67 ± 3.09	2.50 ± 3.55	*ns*
M:F	1 : 5	1 : 2	1 : 4	1 : 2	*ns*

*Age: Tukey HSD shows Moderate LA < NC, $p=.003$, all other comparisons ns. LA Junque Score = Junque Leukoaraiosis Scale Score (score range = 0–40); education = years of education; MMSE = Mini Mental-State Examination; GDS = Geriatric Depression Scale (score of 10 = cut-off for mild depression); M:F = male/female.

Philadelphia (repeatable) Verbal Learning Test (PrVLT)

The PrVLT is a nine-word serial list-learning test with three test versions specifically designed for dementia populations. The PrVLT has been used in our earlier work (Libon et al., 2008; Price et al., 2004), but is described here in detail since it is the primary measure from which our hypotheses are assessed. The PrVLT is similar in design to the nine-word mental status version of the CVLT (Delis, Kramer, Kapla, & Ober, 1999) with the exceptions that (1) the test exemplars were constructed using a corpus of words elicited for a healthy elderly control group whose demographics match the dementia patients under consideration, and (2) the test contains all nine interference list words in the delayed recognition test (for rationale, see Davis, Price, Kaplan, Libon, 2002). The corpus of older-adult category exemplars (e.g., vegetable, fruit, etc.) were generated from 69 cognitively intact community-dwelling elderly volunteers (age $= 77.90 \pm 9.66$). All participants were English speakers and performed normally on basic screening (MMSE < 27 & GDS ≤ 10).[1] There are three versions of the PrVLT. For the current study, each P(r)VLT version was administered randomly and equivalently among participant groups (see Table 2).

The administration and construction of the P(r)VLT is identical to the original 16-word CVLT and the nine-word experimental version of the CVLT (Delis, Kramer, Kaplan, & Ober, 1987; Libon, Mattson, Glosser, & Kaplan, 1996b); i.e., an orally presented nine-word "shopping list" (list A), composed of three items from three categories, is administered five times, followed by an interference (list B) test condition with three words from a category in list A. The interference condition is followed by short delay free and category cued recall test conditions. After a 20-minute filled delay, free recall and category recall are reassessed, followed by a delay recognition test for list A. The recognition test contains 36 words: 9 words from list A (hits), 9 words from list B, 9 prototypic semantic foils, and 9 unrelated words ($n=27$ foils). On the recognition test, participants are asked to indicate if each orally presented word was from list A. Perseverations and Intrusion errors are scored as originally described for the 16-word CVLT

[1] Please contact the authors for more information on P(r)VLT test construction.

Table 2 Group raw unstandardized Philadelphia (repeatable) Verbal Learning Test (P(r)VLT) index mean and standard deviation Scores

	LA group			
	Mild	Moderate	Severe	ND
P(r)VLT Indices				
Immediate free Recall				
List A, Trials 1–5	20.64 (6.41)	21.51 (5.50)	22.30 (7.51)	32.46 (5.20)
Trial 1	3.10 (1.29)	3.23 (1.31)	3.04 (1.22)	4.75 (1.48)
Trial 2	3.99 (1.56)	4.18 (1.53)	4.11 (1.85)	6.00 (1.38)
Trial 3	4.28 (1.46)	4.45 (1.23)	5.00 (1.62)	7.08 (1.21)
Trial 4	4.56 (1.50)	4.70 (1.34)	5.00 (1.90)	7.25 (1.11)
Trial 5	4.71 (1.59)	4.82 (1.30)	5.04 (1.76)	7.79 (1.18)
List B, Interference	2.89 (1.35)	3.16 (1.25)	3.07 (1.90)	4.63 (1.10)
Delay Recall				
Short Delay Free Recall	1.23 (1.35)	1.33 (1.60)	2.48 (2.14)	6.21 (1.72)
Short Delay Cued Recall	2.93 (1.77)	3.07 (1.70)	3.48 (2.03)	6.79 (1.61)
Long Delay Free Recall	0.97 (1.48)	1.21 (1.70)	2.81 (2.59)	6.29 (1.97)
Long Delay Cued Recall	2.25 (1.69)	2.51 (1.76)	3.22 (2.03)	6.83 (1.58)
Intrusion Errors and Perseverations				
Free Recall Intrusion Errors	3.05 (2.88)	1.95 (2.28)	3.07 (3.30)	1.00 (1.47)
Cued Recall Intrusion Errors	5.79 (3.77)	3.51 (3.51)	3.63 (3.21)	0.75 (1.37)
Perseverations	0.65 (1.01)	1.39 (2.56)	1.44 (1.91)	1.29 (1.37)
Recognition Test Performance				
Recognition Hits	7.12 (1.91)	7.07 (1.88)	7.00 (1.94)	8.38 (.82)
Recognition False Positive	10.18 (4.75)	7.23 (4.25)	4.41 (3.04)	0.88 (1.92)
Recognition Error Type				
Semantic	4.43 (2.45)	2.66 (2.26)	1.48 (1.37)	0.33 (.70)
Interference	4.18 (2.24)	3.70 (2.32)	2.63 (2.48)	0.21 (.41)
Unrelated	1.56 (1.80)	0.84 (1.40)	0.26 (.45)	0.00 (.00)

LA = Leukoaraiosis, ND = Non-demented comparison group.

and the nine-word experimental version of the CVLT (Delis et al., 1987; Libon et al., 1996a).

PrVLT Outcome Measures included four composite indices and a select set of error scores (intrusion, word frequency of cued recall errors, perseveration, and recognition foils). The *four factor-based composite indices* (see Table 3) include a Delay Free Recall factor, Immediate Free Recall factor, Intrusion Error factor, and Recognition factor. The test indices comprising each factor were converted to composite *z*-scores referenced to the 24 control participants. *P(r)VLT Free, Cued Recall Intrusions, Perseverations* were scored as originally described for the 16-word CVLT and the nine-word experimental version of the CVLT (Delis et al., 1987; Libon et al., 1996). *PrVLT Word Frequency of Cued Recall Intrusion Errors* was assessed with the Francis and Kucera (1982) corpus. This corpus allowed us to calculated the average word frequency of short and long cued recall intrusions in the English language (a high score indicates greater frequency in the English language). We acknowledge that the original purpose of the Francis and Kucera

Table 3 Factor loadings of P(r)VLT indices using varimax rotation: Eigenvalues and percentage of variance[a]

	Factor loading				
	1 Delay	2 Free	3 Intrusions	4 Recognition	Communality
Long Delay Cued Recall	**.86**	.19	−.09	.03	.74
Long Delay Free Recall	**.85**	.12	−.14	−.05	.70
Short Delay Free Recall	**.85**	.06	−.05	−.03	.77
Short Delay Cued Recall	**.81**	.22	−.05	.05	.78
Interference Free Recall	.10	**.91**	−.16	.01	.71
Total 1–5 Free Recall	.45	**.73**	.13	−.03	.73
Free Intrusions Total	.02	−.16	**.82**	−.16	.86
Cued Intrusions Total	−.22	.10	**.77**	.24	.77
Recognition Hits	.31	.06	−.16	**.81**	.81
Recognition False Positives	−.37	.08	.25	**.77**	.76
Eigenvalues	3.86	1.44	1.23	1.09	
% of variance	38.62	14.43	12.26	10.93	

[a]Principal component analysis using varimax rotation (five iterations) with exclusion of eigenvalues <1.0 assessed the underlying structure of the P(r)VLT indices in the dementia sample. These factors were converted to composite *z*-scores based on the ND sample. The four composites have adequate normative properties for analysis purposes (i.e., Delay Free Recall skewness = .99, kurtosis = .91; Immediate Free Recall skewness = −.11, kurtosis = −.17; Intrusions skewness = −1.11, kurtosis = 2.08; Recognition skewness = .27, kurtosis = −.19).

(1982) corpus was to provide a measure of how frequently words appear in the English language, and that the frequency of a word may not necessarily be the same as its category word frequency. Our decision to use the Francis and Kucera (1982) corpus instead of other lists (e.g., Battig & Montague, 1969), was based on the fact that the 11 semantic categories used in the construction of the three forms of the P(r)VLT were only represented by Francis and Kucera (1982). *P(r)VLT Recognition Errors by Foil Type* (Semantically related, list b-interference, or unrelated) were recorded to examine our hypothesis that LA groups would differ by foil endorsement.

Executive functioning

We compared executive functioning between the three LA groups in order to confirm greater executive difficulty in the severe LA group. The measures used in the composite are: the non-automatized index of the Boston Revision of the Wechsler Memory Scale – Mental Control subtest (WMS-MC; Lamar, Price, Davis, Kaplan, & Libon, 2002; Wechsler, 1945) and test of letter fluency (Benton & Hamsher, 1989). Raw test scores were converted to *z*-scores based on published norms (Lamar et al., 2002; Tombaugh, Kozak, & Rees, 1999, respectively). Standardized scores were averaged to reflect an overall "executive" composite score. Details regarding the composition and scoring of the non-automatized index of the Boston Revision of the WMS-MC subtest can be found in Lamar et al. (2002). Prior research has shown that performance on these tests is very sensitive to

LA severity in patients with mild dementia (Libon et al., 2008; Price et al., 2005). On the letter fluency test patients were given 60 seconds to generate as many words as possible that begin with the given letter of the alphabet, excluding numbers, proper nouns, and the same words with a different suffix. Total correct for each letter were summed for the dependent variable. Imaging studies have shown that letter fluency tests activate the left dorsolateral prefrontal region in younger (Phelps, Hyder, Blamire, & Shulman, 1997) and older adults (Gourovitch et al., 2000).

Statistical analyses

PrVLT factors were converted to *z*-scores based on the ND group scores. A MANOVA assessed LA group differences on the four PrVLT list-learning factors with follow-up via Tukey post-hocs. Paired *t*-tests assessed hypothesized within-group factor differences (PrVLT Immediate versus Delay; Delay versus Recognition) and a one-way ANOVA confirmed LA group differences in false positive errors. For non-normalized data, non-parametric analyses assessed hypothesized LA between- and within-group error differences (intrusion, cued recall intrusion frequency, perseveration, and recognition foil types). One-way ANOVAs confirmed greater executive dysfunction in the severe LA group. PrVLT analyses report eta, Cohen's *d* (Cohen, 1988). Significance was set at $p \leq .01$.

RESULTS[2]

LA group differences on P(r)VLT *z*-score composite indices

A MANOVA identified a main LA group effect on a linear combination of the four P(r)VLT *z*-score composite factors, Wilk's $\lambda = .777$, $F(137, 274) = 4.61$, $p < .001$, $\eta = .35$. Resulting follow-up univariate ANOVAs were significant for Delay Free Recall, Recognition, and the Intrusion composite factors: Delay Free Recall $= F(2, 140) = 5.51$, $p = .005$, $\eta = .27$; Intrusions $= F(2, 140) = 6.95$, $p = .001$, $\eta = .30$; Recognition $= F(2, 140) = 12.20$, $p < .001$, $\eta = .38$. For the Delay Free Recall factor, the mild and moderate LA groups scored lower than the severe group (Delay Free Recall *z*-score mean $\pm$ SD: mild LA $= -2.72 \pm 0.78$; moderate LA $= -2.62 \pm 0.84$; severe LA $= -2.07 \pm 1.17$, $ps \leq .01$; mild to severe $d = 0.65$; moderate to severe $d = .54$). For the Intrusion factor, the mild LA group scored lower (producing greater numbers of intrusion errors) than the moderate LA group (Intrusion mean $\pm$ SD: mild LA $= -2.63 \pm 1.91$; moderate LA $= -1.34 \pm 1.72$; severe LA $= -1.79 \pm 1.91$, $p < .001$; mild to moderate $d = 0.71$). For the Recognition factor, the mild LA group scored lower than the other two LA groups ($p < .001$; mild to moderate $d = 0.52$; mild to severe $d = 1.13$). There was a trend for the moderate group to score lower than the severe group ($p = .03$; Recognition *z*-score mean $\pm$ SD: mild LA $= -3.18 \pm 1.24$; moderate

[2] Some readers may question whether lacune presence altered the PrVLT factor structure or results. We re-examined these data after excluding patients with lacunes (new sample: mild LA $n = 57$, moderate LA $n = 26$, severe LA $n = 2$). The PrVLT factor structure remained the same with the exception of a slightly lower percent variance (new cumulative percentage = 74.13). Result findings were unchanged.

LA = −2.47 ± 1.49; severe LA = −1.75 ± 1.28; moderate to severe $d = 0.52$). As predicted, the severe LA group performed best on delayed recognition testing, with the Mild LA group producing many intrusion errors and the worst group performance on recognition.

Within-group factor composite comparisons: Immediate Free Recall vs Delay Free Recall; Delay Free Recall vs Recognition Composite Comparison

Only the mild and moderate LA groups scored lower on the Delay Free Recall compared to the Immediate Free Recall (both $p < .001$; mild $d = 0.83$; moderate $d = 1.05$) suggesting poor retention. The mild LA group also scored lower on the Recognition index relative to Delay Free Recall ($p = .002$; $d = 0.44$) suggesting a failure to benefit from recognition testing. Thus, in addition to distinct group differences, these findings identify meaningful performance patterns within each LA group.

Group and intrusion frequency (free vs cued)

LA groups only differed in total number of cued recall intrusions, cued recall: Kruskal Wallace: $\chi^2(2) = 16.60$, $p < .001$; free recall, $p > .05$. As predicted, the mild LA group produced more cued recall intrusions than the moderate and severe group (both $p < .001$; mild to moderate $d = 0.63$; mild to severe $d = 0.62$).

Word frequency of cued recall intrusions (short and long delay combined, see Method)

LA groups differed in cued recall intrusion word frequency as measured with the Frances and Kucera corpus, Kruskal Wallace, $\chi^2(2) = 13.88$, $p < .001$. The mild LA group produced intrusions that were more frequent in the English language compared to the other LA groups (all p values $\leq .002$; mild to moderate $d = 0.54$; mild to severe $d = 0.64$).

Perseverations

Contrary to our prediction, LA groups did not differ on total number of perseverations, Kruskal Wallace, $\chi^2(2) = 2.37$, *ns*.

Recognition false positives and foil endorsements

Analyses assessed for group differences in error and type of foil endorsement. Response bias to list B recognition foils may suggest a source recall problem signifying executive difficulties, while equal endorsement of all types may indicate a profound amnestic impairment.

One-way ANOVA confirmed a between-group difference in false positive foil endorsement, $F(2, 140) = 20.24$, $p < .001$, $\eta = .47$. The mild LA group

produced many more false positives than the other two LA groups (both $p < .001$; mild to moderate $d = 0.65$; mild to severe $d = 1.45$), and the moderate more than the severe LA group ($p = .001$; $d = 0.76$).

Between-group analyses of foil type were significant (Kruskal Wallace, all $p < .006$); the mild LA group significantly endorsed more semantic and unrelated foils than the moderate LA group (U test, $p < .001$, $p = .01$, respectively; semantic $d = 0.75$; unrelated $d = 0.45$), and more recognition foils of all types (semantic, list B interference, unrelated) than the severe LA group (U test, all $p \leq .002$; semantic $d = 1.49$; interference $d = 0.66$; unrelated $d = 0.99$). *Within-group analyses of foil type* shows that the moderate LA group significantly endorsed more list B interference relative to semantic foils, Wilcoxon sign test, $p = .01$; $d = 0.45$, and that all groups endorsed many more semantic and list B foils relative to unrelated foils ($p < .001$, all comparisons, all Cohen's $d < 1.0$). These findings suggest that the mild LA group's poor recognition index performance differed from the other LA groups by an over-endorsement of all foil types. A significant predilection for list B foils was only observed for the moderate LA group.

LA group and "executive function" impairment

One-way ANOVA yielded a main effect of LA group, $F(2, 139) = 13.83$, $p < .001$, $\eta = .41$. Tukey tests show the severe LA more impaired than mild or moderate LA on the composite of executive function (mean ± SD: severe LA: -2.52 ± 1.29; moderate LA: -1.67 ± 1.37; mild: -1.15 ± 0.96, p values $\leq .009$).

DISCUSSION

This study indicates that a group of dementia patients with a relatively cohesive clinical picture involving insidious onset with no evidence of stepwise decline, ADL/IADL difficulties, memory difficulties (at least from a superficial perspective involving family report), and impairment in at least one other cognitive domain, can exhibit differing verbal serial list-learning profiles based solely on leukoaraiosis (LA) severity groupings. Individuals with very little to no LA exhibited the most striking list-learning impairment with characteristics of a classic amnesic profile. Relative to this group, individuals with severe amounts of LA performed substantially better on the delay and recognition indices and error analyses. These findings are most synonymous with a dysexecutive profile, although hypothesized increases in perseverations and increased recognition list B interference foils were not observed. Individuals with moderate LA produced elements of both amnesic and dysexecutive profiles. These distinct list-learning profiles show that LA is not representative of a single, continuous disease state but likely represent distinct dementia syndromes.

The mild LA group demonstrated the clearest amnesic profile on composite comparisons and error analyses. Despite a comparable level of impairment among the three LA groups on the immediate free recall in list A test trials, individuals with mild LA (where LA is estimated to be in 10% or less of the white matter) demonstrated significant forgetting such that performance declined after a delay. Recall was not aided by recognition testing. These patients also

produced numerous intrusion errors, particularly on cued recall testing. These types of intrusions have been functionally associated with the left (Desgranges, et al., 2002) and bilateral (Lekeu et al., 2003) parahippocampal regions using PET methodology. Moreover, the mild LA group produced more generic intrusions such as "dog" or "apple". This suggests greater disruption of associative semantic processes mediated by either lateral or medial temporal lobe dysfunction (Hodges, Patterson, Oxbury, & Funnell, 1992; Warrington, 1975). A recent French study by Canolle et al. (2008) also reports that category intrusions were more prototypic among individuals with Alzheimer's disease.

Additionally, because our list-learning paradigm contained equal numbers of recognition foil types we were also able to directly examine recognition error endorsement. In addition to failing to benefit from recognition testing, the mild LA group produced numerous false positives with no significant response bias to recognition semantic or list B interference foils. They also endorsed many unrelated foils compared to individuals with moderate or severe LA. This liberal "yes" response suggests memory impairment beyond that of proactive interference (Davis et al., 2002). Overall, the mild LA group's pattern reveals compromised learning, loss of information over a delay, failure to benefit from recognition testing, and evidence of semantic/lexical disturbance. This pattern is most suggestive of pathology involving the medial temporal lobe, such as would be seen in pathologically pure Alzheimer's disease.

The severe LA group, by contrast, produced the most dysexecutive profile. Despite similar immediate memory performance to those with lesser LA, this group outperformed the other two LA groups on delay and recognition testing. They also produced few cued recall intrusions and recognition foil distractors. This performance pattern, coupled with their striking impairment on executive tests (range of one to two standard deviations below the other two groups) underscores the hypothesis that memory difficulties associated with severe LA is dysexecutive in nature. However, the severe LA group did not produce significantly more perseverations or recognition interference foils as hypothesized. Future studies should compare severe LA dementia patients to classically defined subcortical diseases (e.g., PD) on list-learning paradigms in order to determine the actual extent of this dysexecutive profile. We also encourage future study of location of LA in the deep versus more surface (u-fiber) regions, and which health risk factors (e.g., vascular) predict severity of LA in this group.

The moderate LA group demonstrated a mixed memory profile with both amnesic and dysexecutive traits. They scored lower on the delay index relative to the immediate recall index, yet produced few intrusion errors. They also endorsed more semantic and list B foils than the severe LA group, and a comparison of their own within group foil response bias suggests that they were overly pulled to the list B interference foils. Moderate LA appears to mark mixed cortical and subcortical pathologies.

We believe that our choice to ignore traditional dementia diagnosis (AD, sVD) and focus on LA severity groupings was experimentally and theoretically beneficial. First, it allowed us to examine the differential role of LA on list-learning profiles without prejudice of dementia diagnosis based partially on neuropsychological and neuroradiological data. Second, we have preliminary

clinical evidence that LA is not necessarily a progressive disease state. At least in individuals with similar dementia severity, LA can manifest in different amounts. Third, when combined with neuropsychological testing, LA severity may foretell underlying pathology and have therapeutic implications. Recent research suggests that individuals with greater amounts of LA and a more dysexecutive profile may benefit most from acetylcholinesterase inhibitors such as donepezil (e.g., Thomas, Libon, Ledakis, 2005). Bypassing diagnostic criteria in favor of combined neuropsychologic and neuroradiologic profiles appears relevant given growing awareness that vascular dementia includes a heterogeneous group of cognitive disorders (Jellinger & Attems, 2007) and the dominance of mixed dementias in medical settings.

Indeed, there is growing evidence that LA can have distinct radiological and pathological patterns. LA presenting as confluent on MRI (widespread throughout the deep white matter) has been shown to be progressive, while punctuate LA (isolated regions on MRI) is not (e.g., Gouw, et al., 2008; Sachdev, Wen, Chen, & Brodaty, 2007). Sjobeck, Haglund, and Englund (2006) found that neuropathologically pure AD brains with LA showed primary bifrontal loss of oligodendrocytes despite no other vascular components. They speculate that this bifrontal pattern may clinically associate with executive dysfunction and incorrectly lead clinicians to a diagnosis of vascular dementia. There are also reports that LA is associated with reduced vascular integrity both in and beyond the LA lesion in the white matter (e.g., Brown, Moody, Thore, Challa, & Anstrom, 2007; Young, Halliday, & Kril, 2008). Within these regions LA has variable vascular densities, which may affect the brain globally with capillary loss while not necessarily leading to infarction of tissue (Brown et al., 2007). In some research, overall severity of LA associates with the degree of cortical (Capizzano et al., 2004) and medial temporal atrophy (van der Flier et al., 2005; but note contrary evidence reported by Brun & Englund, 1986; Sjobeck & Englund, 2003).

Questions about topographical location of LA and regional association in cortical changes have been raised (Sjobeck et al., 2006), yet the issue still needs clinical investigation. White matter fibers have many multi-modal and limbic regions (Filley, 2001); LA near white matter u-fibers may have distinct clinical and pathological characteristics from that in the deep white matter. While there are a growing number of sophisticated pathology studies examining regional LA in periventricular and deep regions by lobe (e.g., Young et al., 2008), there remain few studies integrating neuropsychological patterns with MRI LA location severity or pathology. We are expanding our studies to examine these issues, and encourage other investigators to do so as well.

We acknowledge limitations in our current study. The 40-point Junque LA scale, as well as any other MRI visual rating scale, is best viewed as only a proxy of true white matter involvement. The means by which we operationally measured LA, therefore, is semi-quantitative and provides only an approximate estimate of LA involvement. Another limitation was that we had limited availability to medical information that could have potentially shed light on the underlying etiology of MRI-LA (i.e., hypertension, diabetes). This study also did not assess dissociations between LA and other imaging variables such as

hippocampal volume and cortical thickness. While we identified that the presence or absence of lacunae did not alter the overall results of the study (see footnote 2), region of lacunae was not accounted for in the current analyses and may provide important information. Finally, we recognize that our control group for the PrVLT is small and thus serves only as a preliminary normative reference set for dementia. A larger control group that has imaging data as well will be beneficial for future studies. Despite these caveats we believe that the current research provides convincing evidence that LA severity can be associated with distinct patterns of impairment on episodic memory tests.

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