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Alterations in working memory as a function of leukoaraiosis in dementia

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Abstract

Dementia research suggests executive dysfunction is best understood within the context of disease-specific neuropathology. Leukoaraiosis (LA) results in executive dysfunction yet little is known about its impact on specific aspects of working memory (WM). This study aimed to investigate the relationship between MRI LA severity and WM in dementia. A visual rating scale was used to assign patients with dementia into groups with minimal-mild LA (Low LA; $n=34$) and moderate-severe LA (High LA; $n=32$). A modified Digit Span Backward Task consisting of 3-, 4-, and 5-span trials measured specific components of WM. Short-term storage and rehearsal in WM were assessed by the total number of digits reported regardless of recall order (ANY-ORDER; e.g., 47981 recalled '18943', score = 4). Mental manipulation in the form of disengagement and temporal re-ordering was assessed by the total number of digits recalled in correct position (SERIAL-ORDER; e.g., 47981 recalled '18943', score = 3). There was no difference between LA groups on ANY-ORDER comparisons. The High LA group obtained lower SERIAL-ORDER scores than the Low LA group. Stepwise regression analyses were conducted that first entered MMSE scores then composite *z*-scores reflecting executive functioning, language and memory. ANY-ORDER performance variance was explained solely by dementia severity. SERIAL-ORDER performance variance was further explained by executive dysfunction. Results suggest that high degrees of LA do not interfere with immediate (digit) recall but do interfere with disengagement and temporal re-ordering. LA may disconnect the frontal lobes from subcortical and cortical structures that form the neuronal networks critical for these WM functions.

Keywords: Working memory; Executive functioning; Alzheimer's disease; Vascular dementia; Subcortical dementia

Advances in neuroradiology and large-scale autopsy studies suggest that Alzheimer's disease (AD) and subcortical ischemic vascular dementia (VaD) may overlap with regard to subcortical neuropathology (Jellinger, 2002a; Pantoni & Garcia, 1997). MRI evidence of leukoaraiosis (LA) or white matter alteration is one of several subtype of vascular disease associated with dementia (see Cosentino et al., 2004; Pantoni & Garcia, 1997; Pantoni & Inzitari, 1998 for reviews). Risk factors for vascular disease and subsequent LA are associated with cognitive impairment that increases the risk for both AD and VaD (Au et al., 2006). LA involving the periventricular and deep white matter tracks is often linked with a clinical diagnosis of VaD; however, LA in these regions also occurs in AD (Burns et al., 2005; Gurol et al., 2006). Recent studies show that upwards of 40% of pathologically confirmed AD cases also present with significant LA (Merino & Hachinski, 2000; Yip et al., 2005). Furthermore, over 30% of patients diagnosed with VaD have concomitant AD (see Kalaria & Ballard, 1999 for review). The presence of LA as seen on MRI scans influences the symptoms, signs and course of dementia regardless of diagnosis (Jellinger, 2002a, 2002b; Luchsinger et al., 2005) particularly as it relates to cognitive and executive dysfunction within attention, infor-

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mation processing and working memory (Burns et al., 2005; Desmond, 2004; Price, Jefferson, Merino, Heilman, & Libon, 2005).

The cognitive and executive dysfunction associated with LA may be induced by cortical–subcortical and cortical–cortical disconnections (Catani & ffytche, 2005). Previous work in our laboratory suggests that pervasive executive dysfunction seen in dementia (e.g., deficits encompassing both higher-level and more basic executive skills), may be associated with pervasive disease-related neuropathology affecting afferent and efferent connections linking the prefrontal cortices with other areas of brain involved in these processes (Freeman et al., 2000; Giovannetti et al., 2001; Lamar et al., 1997; Lamar, Swenson, Kaplan, & Libon, 2004). This theory, based on the work of Luria (1980) and Goldberg and Bilder (1987), does not require frank frontal lobe lesions for the manifestation of varying levels of executive dysfunction in dementia despite the fact that specific aspects of executive dysfunction such as working memory have been ascribed to regions within the prefrontal cortex.

Studies of patients and monkeys with discrete lesions first localized working memory to the prefrontal cortex (Jacobsen, 1936; Milner, 1963). Furthermore, physiological studies have revealed that there are neurons in the frontal lobe that sustain discharges after stimulus presentation and short-term or immediate recall (Fuster & Alexander, 1971) and this activity might allow memory representations to persist and be manipulated. Several neuroimaging studies have further supported the postulate that there are distinct storage, rehearsal and manipulation components of working memory but only those components related to higher order executive abilities may be attributed to the prefrontal cortex. Brodmann's areas 40 (supramarginal gyrus) and 7 (superior parietal lobe) have been associated with the storage of verbal information while Brodmann's area 45, also known as Broca's area, appears to be responsible for the rehearsal of verbally mediated information (Paulesu, Frith, & Frackowiak, 1993; Smith, Jonides, Marshuetz, & Koeppe, 1998). Brodmann's area 46 or the dorsolateral prefrontal cortex has been associated with the successful manipulation and inhibition of information (Collette, Van der Linden, & Salmon, 1999; D'Esposito et al., 1998); working memory functions typically associated with higher-level executive abilities.

Given increasing evidence suggesting the role of LA in various forms of dementia as well as executive dysfunction, the current study aimed to characterize patients' working memory deficits as a function of the severity of MRI LA independent of the clinical form of their associated dementia. We hypothesize that the severity of LA will influence the type of working memory deficits observed among patients with dementia regardless of clinical diagnosis. We predict that, when compared to participants with a low degree of LA, participants with a high degree of LA will show higher-level mental manipulation working memory deficits as opposed to less complex rehearsal and immediate recall deficits. By using LA as the independent variable rather than diagnostic criteria, we will be better able to examine how LA directly affects specific aspects of executive functioning and working memory in dementia.

1. Methods

1.1. Participants

Participants included in the current research were originally patients of the UMDNJ-SOM New Jersey Institute for Successful Aging Memory Assessment Program (MAP). All MAP patients receive an examination by a social worker, neuropsychologist, and geriatrician. A brain MRI and appropriate diagnostic laboratory studies were obtained to evaluate for reversible causes of dementia. A clinical diagnosis of dementia was determined for each patient at an interdisciplinary team conference. This study was approved by the UMDNJ-SOM institutional review board with consent obtained according to the Declaration of Helsinki.

We included a total of 66 participants in the current study. Twenty-eight participant met criteria for NINCDS-ADRDA probable AD (McKhann et al., 1984), 20 participants met criteria for probable/possible VaD using the California Criteria of Chui (Chui et al., 1992) and 18 participants were diagnosed with a mixed AD/VaD dementia as determined on the basis of the MAP inter-disciplinary team conference. Participants were excluded if there was any history of head injury, substance abuse, major psychiatric disorders including major depression, epilepsy, B12, folate, or thyroid deficiency. This information was gathered from a knowledgeable family member.

1.2. MRI protocol and participant groups

A 1.5 T Siemens MRI scanner was used to obtain T1-weighted (TR-500 ms, TE-9 ms) and FLAIR (TR-8500 ms, TE-99 ms) images with a 5 mm slice thickness and 1 mm gap between slices. The severity of white matter alterations was quantified using the 40-point Leukoaraiosis (LA) Scale of Junque (Junque et al., 1990; Pujol, Junque, Vendrell, Capdevila, & Marti-Vilalta, 1991); a MRI visual rating scale similar to several other scales found in the literature (Scheltens et al., 1993; Wahlund et al., 2001; Ylikoski et al., 1993). We chose to measure MRI LA with the Junque scale because its range of measurement (i.e., 0–40) permits statistically robust analyses. A board-certified neuroradiologist blinded to all clinical data as well as dementia diagnosis graded white matter in five specific areas for each hemisphere, i.e., 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. Scores for each area, ranging from 0 (no visible white matter alterations) to 4 (severe white matter alterations), were summed for a total LA scale score (total score = 40).

Currently, there is no absolute consensus offering concrete guidelines for the operational definition of the clinical significance of MRI LA. We elected to follow procedures by Roman et al. (1993) who have suggested that 25% of WM may need to be involved before these changes in the white matter influence the clinical signs associated with dementia. Following these guidelines, participants in the current study were placed in the Low LA group if their LA scale was less than or equal to 9, that is, involving approximately no more than 25% of WM alterations as measured with the 40-point LA scale ($n = 34$; 4.1 ± 3.1 or 10.2%). The High LA group consisted of individuals with LA scales of 10 or greater, that is, more than 25% WM alterations ($n = 32$; 17.8 ± 6.5 or 44.5%) as measured from FLAIR-weighted MRI studies. The criterion validity of the Junque scale to group participants in this fashion is reported elsewhere (Price et al., 2005).

Groups did not differ in terms of sex distribution or years of education; however, there were differences in other demographic variables (Table 1). Separate one-way analyses of variance (ANOVA) revealed between-group differences on age ($p = 0.007$), level of dementia as assessed with the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1974) $p = 0.02$) and level of depression as measured with the Geriatric Depression Scale (GDS; Yesavage, 1988) $p = 0.006$). The High LA group was older, performed worse on the MMSE and reported more depressive symptomatology than their Low LA counterparts. As expected, Junque scale scores also differed between-group.

Bivariate Pearson's correlations were conducted between age, MMSE, GDS and our dependent variables of interest. Neither age nor GDS correlated significantly with dependent variables of interest ($p > 0.01$) however, MMSE scores did significantly correlate with the majority of dependent variables of interest ($p \leq 0.01$). As a result of this preliminary analysis showing the

Table 1
Demographic information

	Low LA, M (S.D.)	High LA, M (S.D.)
n	34	32
Age (years)**	77.5 (5.7)	81.3 (5.2)
Education (years)	12.3 (2.1)	12.1 (2.6)
MMSE*	22.5 (2.8)	20.5 (3.9)
GDS**	2.5 (2.6)	4.7 (3.5)
Junque scale***	4.1 (3.1)	17.8 (6.5)
Sex (M:F)	5:29	10:22

*$p < 0.05$; **$p < 0.005$; ***$p < 0.001$. *Note*: MMSE = Mini-Mental State Examination; GDS = Geriatric Depression Scale.

significant relationship between MMSE scores and our dependent variables of interest in the current study, the MMSE was entered as a covariate in all analyses. While the presence of clinical depression has been associated with alterations of frontal lobe activity (Mayberg, 1994), we did not covary for GDS given there was no relationship of this variable to other variables of interest. Furthermore, not only were scores low and well below accepted cut-offs used to diagnosis a clinical depression, formal clinical interviews with patients and their family did not provide evidence of a clinical depression in any study participant.

1.3. Working memory procedure

We assessed working memory with a modified Digit Span (DSp) Backward paradigm taken from the WAIS-R (Wechsler, 1981). In reviewing the dementia literature concerning performance on the WAIS-R Digit Span subtest, it is evident that the majority of studies show performance deficits for the more executively demanding DSp-Backward trials as opposed to the simpler attention-driven DSp-Forward trials (Kramer et al., 2003; Lam, Lui, Chiu, Chan, & Tam, 2005). Furthermore, the Backward portion of the WAIS-R Digit Span subtest has been included in several screening tools for detecting mild cognitive impairment and early forms of dementia (Kalbe et al., 2004; O'Sullivan, Morris, & Markus, 2005). Thus, we devised an experimental backward digit task (BDT) that would measure various components of working memory with the expectation that this strategy will result in a more subtle exploration of the specific working memory deficits associated with LA in patients with dementia.

1.4. Backwards Digit Task (BDT)

The BDT (Table 2) consists of seven trials of 3-, 4- and 5-digit span lengths for a total of 21 trials. All 4- and 5-span trials were constructed so that contiguous numbers were placed in strategic positions. For example, in 4-span trials contiguous numbers were placed in either the first and third or second and fourth digit positions, e.g., 5269 or 1493. In 5-span trials contiguous numbers were also placed in the middle three digits positions, e.g., 16579. Three-span test trials were not constructed in this fashion because of primacy and recency effects.

Table 2
Backward Digit Task example trials

3-Span trials
(1) 2-4-8
(2) 5-9-3
(3) 4-2-7
4-Span trials
(1) 1-3-9-4
(2) 6-2-7-9
(3) 4-7-5-2
5-Span trials
(1) 9-6-7-5-1
(2) 2-7-8-6-4
(3) 8-5-6-4-1

The BDT was administered using standardized WAIS-R DSp-Backward procedures with the exception that the discontinuation rule was not applied as all patients received all 21 test trials of the BDT.

The following dependent variables were scored from the same corpus of BDT trials in which patients were instructed to say the digits they heard in reverse order:

(1) *Percent of BDT correct SERIAL-ORDER*. This score reflects the total number of digits correctly recalled in accurate serial position divided by the total possible correct multiplied by 100, [(total # correct digits SERIAL-ORDER)/(total possible correct)] × 100. This variable is believed to measure the more executively demanding aspects of working memory associated with mental manipulation such as disengagement and temporal re-ordering.
(2) *Percent of BDT correct ANY-ORDER*. This score reflected the sum total of every digit correctly recalled regardless of serial position divided by the total possible correct multiplied by 100, [(total # correct digits ANY-ORDER)/(total possible correct)] × 100. By eliminating the importance of serial position during digit recall despite instruction, this variable is believed to reflect less complex aspects of working memory characterized mainly by short-term or immediate storage and rehearsal mechanisms.

Additional BDT errors were scored on the basis of digit span scoring procedures previously suggested by Kaplan, Fein, Morris, and Delis (1991) and associated with executive functioning and working memory (Lamar et al., 1997; Stuss, Shallice, Alexander, & Picton, 1995). These qualitative errors were scored regardless of positioning and included:

(3) *Capture errors*. This score reflected the sum total of two types of capture errors. The first type, *Within Trial Capture Errors*, were coded when on 4- and 5-span trials participants grouped contiguous numbers in serial order, i.e., 1493 – '3491' or '3419'; 16579 – '95671' or '96751'. The second type of capture error consisted of *Between Trial Capture Errors*. This type of capture error was coded on 3-, 4- and 5-span test trials when participants incorporated a digit or digits from either the immediately preceding test trial or two test trials prior to create contiguous numbers in a serial order.
(4) *Perseverations*. This error type was coded on 3-, 4- and 5-span test trials when patients repeated a digit within a given trials, i.e., 16579 – '97569'. The number reflects the presence of a perseveration as opposed to the number of times a particular digit is repeated.
(5) *Intrusion errors*. In very rare instances patients might erroneously report a digit that was not part of the immediate test trial and not part of the test trial either one or two test trials prior.
(6) *Total errors*. The total of all error types previously delineated (#1–5) were summed for an overall total error score. Thus, all capture errors, perseverations and intrusions were summed along with errors of SERIAL-ORDER and ANY-ORDER to provide an index of total errors on the BDT.

1.5. Neuropsychological assessment

Three cognitive domains were assessed with individual neuropsychological test measures: executive functioning, language and memory. A domain composite score was created on the basis of an average of normative based *z*-scores. Prior to calculating the composite scores, we ensured that the direction of all individual test *z*-scores reflected the same level of performance, i.e., the higher the *z*-score the better the performance:

(1) *Executive functioning*. Three tests were administered including the Boston Revision of the Wechsler Memory Scale-Mental Control subtest (Lamar, Price, Davis, Kaplan, & Libon, 2002), letter fluency (letters 'FAS'; Spreen & Benton, 1969; Spreen & Strauss, 1998) and clock drawing to command and copy (Goodglass & Kaplan, 1983).

The Boston Revision of the Wechsler Memory Scale-Mental Control subtest (Lamar et al., 2002). In addition to the three tasks that comprise the standard Wechsler Memory Scale-Mental Control subtest (i.e., counting from 20 to 1, reciting the alphabet, and adding serial 3's; (Wechsler, 1945), four additional tasks were included: reciting the months of the year forward and backward, an alphabet rhyming task which requires patients to identify letters that rhyme with the word "key", and an alphabet visualization task, which requires patients to provide all block printed letters that contain

curved lines. The dependent variable derived from this test was an accuracy index (AcI) derived from the three non-automatized tasks (i.e., months backward, alphabet rhyming, and alphabet visualization). This accuracy index was based on the following algorithm: AcI = [1 − (false positive + misses/# possible correct)] × 100. This algorithm yielded a percentage score ranging from 0 to 100, such that patients obtaining a score of 100% correctly identified all targets and made no false positive responses. A composite score assessing performance on all non-automatized mental control tasks were calculated by averaging the AcI for three tasks for each patient. Select subtests have been shown to activate dorsolateral prefrontal regions in healthy younger adults (Wildgruber, Kischka, Ackermann, Klose, & Grodd, 1999).

Letter fluency (Spreen & Benton, 1969; Spreen & Strauss, 1998). Using the letters 'FAS', participants were given 60 s to generate words, excluding proper nouns, beginning with a specified letter. The dependent variable was the total number of responses summed across each letter. This measure assesses verbal fluency, spontaneous flexibility and cognitive persistence (Carew, Lamar, Cloud, Grossman, & Libon, 1997; Spreen & Strauss, 1998) and has been shown to activate left dorsolateral prefrontal cortex in older adults (Gourovitch et al., 2000; Mummery, Patterson, Hodges, & Wise, 1996).

The Clock Drawing Task (Goodglass & Kaplan, 1983). Participants were asked to draw the face of a clock with the hands set for "10 after 11" to command and copy. Following procedures described by Libon, Malamut, Swenson, Sands, and Cloud (1996), 10 error types related to graphomotor impairment, errors in hand/number placement, and errors related to executive control impairment were scored as either 1 (i.e., present) or 0 (i.e., absent). Performance in the command and copy conditions was scored separately. The dependent variable was the total number of errors summed across the command and copy conditions. Multiple studies of normal and pathological aging suggest that clock drawing can provide a measure of executive dysfunction involving organization and planning and should be considered an executive task (Cosentino et al., 2004; Lamar, Price, et al., 2002; Lamar, Zonderman, et al., 2002; Libon et al., 1996; Libon, Swenson, Barnoski, & Sands, 1993).

(2) *Language functioning and lexical retrieval*. Two tests were administered including the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983) and the 'animal' word list generation (Carew et al., 1997; Monsch et al., 1992).

The Boston Naming Test (BNT; Kaplan et al., 1983). This test is comprised of 60 line drawings for confrontational naming. Semantic and phonemic cues were provided should a participant be unable to name a particular item. The dependent variable derived from the BNT was the number of correct responses during initial confrontational naming.

The Word List Generation Task (WLG; Monsch et al., 1992), Participants were given 60 s to generate animal exemplars. The dependent variable from the 'animal' WLG task was the total number of responses produced during the time allotted. Several positron emissions tomography studies of category fluency suggest increases in regional cerebral blood flow within left temporal cortex hypothesized to house semantic stores of information (Gourovitch et al., 2000; Mummery et al., 1996).

(3) *Verbal declarative memory*. This area of cognition was assessed with the Philadelphia (repeatable) Verbal Learning Test (PrVLT; Garrett et al., 2004; Libon, Price, Garrett, & Giovannetti, 2004; Price et al., 2002; Price et al., 2004). The P(r)VLT is modeled after the California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1987; Libon, Malamut, et al., 1996; Libon, Mattson, et al., 1996) and consists of a 9-word list drawn from three semantic categories, administered over five trials (list A). A 9-word interference list is then administered (list B) followed by a category cued recall condition for list A. Short and long delayed free and category recall for list A and delayed recognition are assessed. For the present research three P(r)VLT indices were analyzed: delayed free recall, extra-list intrusion errors from the two category-cued recall test conditions, and a delayed recognition discriminability index. These indices were chosen because previous research with dementia patients has shown that these indices load on separate factors and, therefore, appear to assess different aspects of declarative memory (Price et al., 2004).

1.6. Statistical analyses

All variables were tested for normality through an examination of skewness, kurtosis and the more stringent Kolmogorov–Smirnov statistic with a Lilliefors significance level. As a result, we analyzed the data using the parametric and non-parametric procedures outlined below. To examine the hypothesis that a high degree of LA will induce mental manipulation deficits in disengagement and temporal re-ordering versus immediate stimulus (digits) recall deficits, a 2 × 2 repeated measures ANCOVA was used to assess for differences between the High and Low LA groups based on the two BDT variables, i.e., percent correct in ANY-ORDER thought to reflect short-term storage by using rehearsal and/or echoic storage after stimulus presentation and percent correct in SERIAL-ORDER that in addition to short-term storage requires disengagement from the stimulus presentation order and temporal re-ordering controlling for MMSE. Follow-up analyses were conducted when appropriate. Follow-up analyses related to span length were also conducted. A univariate ANCOVA investigated group differences (High LA versus Low LA) on total errors, regardless of span length, with follow-up analyses investigating group differences in individual span length (3, 4, and 5). Where appropriate, the non-parametric Mann–Whitney *U*-test detailed the role of individual qualitative error types included in the total error calculation.

Separate regression analyses were conducted to support our assertion that the two BDT percent correct order variables, ANY-ORDER and SERIAL-ORDER, as mentioned above related to different aspects of executive functioning. Thus, after entering MMSE scores into each regression model, a stepwise procedure was used for the composite *z*-scores or predictor variables representing executive functioning, language and memory. As we were most interested in the role of executive functioning on the BDT variables, we did not measure other subtle aspects of cognition that may be influencing performance outside of the major divisions described above.

Lastly, we ran separate one-tailed partial correlations controlling for MMSE between the severity of LA as measured by the 40-point Leukoaraiosis Scale of Junque (Junque et al., 1990; Pujol et al., 1991) and the ANY-ORDER and SERIAL-ORDER BDT variables. We also correlated the severity of LA with composite indices of executive functioning, language and memory. We performed these partial correlations controlling for MMSE to examine the relationship between LA and other cognitive functions.

2. Results

2.1. Order analyses

The 2 (High LA versus Low LA) × 2 (ANY-ORDER versus SERIAL-ORDER) ANCOVA controlling for MMSE revealed a significant group × order interaction, $F(1, 63) = 12.16$, $p = 0.001$, and significant main effects for group, $F(1, 63) = 7.97$, $p = 0.006$, and order, $F(1, 63) = 21.25$, $p < 0.001$ (Fig. 1). Follow-up analyses revealed that the Low LA group outperformed the High LA group only on SERIAL-ORDER performance [Low LA: 77.9 + 13.2; High LA: 64.0 + 15.5; $F(1, 63) = 10.48$, $p = 0.002$].

2.2. Follow-up span length analyses

We conducted a series of univariate ANCOVAs with group (High LA versus Low LA) as the between-group variable and span length (3-span SERIAL-ORDER, 4-span SERIAL-ORDER and 5-span SERIAL-ORDER) as separate within-group variables controlling for MMSE. This series of analyses revealed that the Low LA group outperformed the High LA group across all span lengths tested (Table 3). Thus, the Low LA group recalled more digits in serial order than their High LA counterparts for 3-span [$F(1, 63) = 8.73$, $p = 0.004$], 4-span

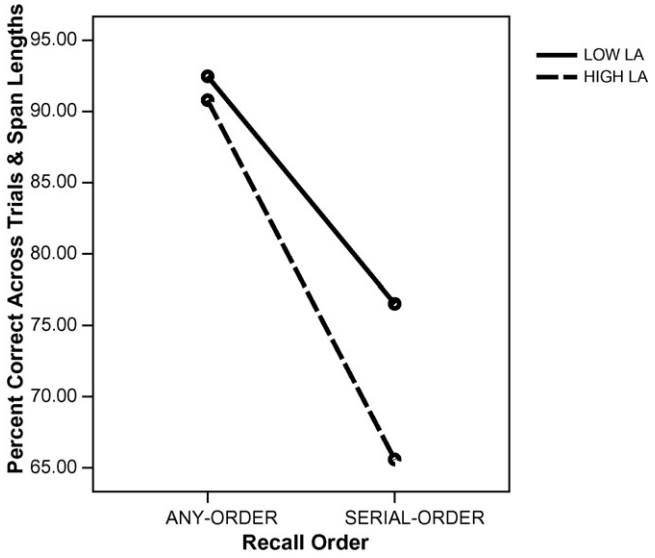

Fig. 1. ANY-ORDER and SERIAL-ORDER performance during the Backward Digit Task for High and Low LA groups.

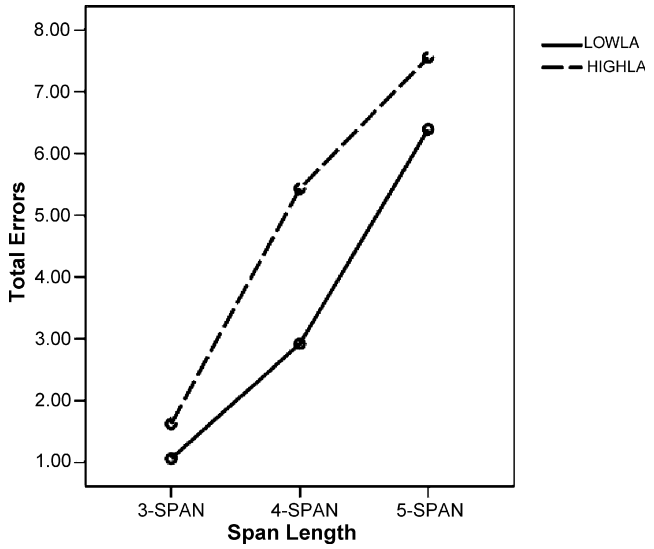

Fig. 2. Total errors by span length for High and Low LA groups.

[F(1, 63) = 10.17, $p = 0.002$] and 5-span lengths [$F(1, 63) = 4.06$, $p = 0.04$].

2.3. Total error analyses

A univariate ANCOVA assessing group (High LA versus Low LA) differences between total errors produced while controlling for MMSE revealed a significant effect of group with the High LA group committing more total errors than the Low LA group, $F(1, 63) = 8.29$, $p = 0.005$; Table 3.

2.4. Follow-up span length analyses

We conducted a series of univariate ANCOVAs with group (High LA versus Low LA) as the between-group variable and span length (3-span total errors, 4-span total errors and 5-span total errors) as separate within-group variables controlling for MMSE (Table 3). This series of analyses revealed that the High LA group produced significantly more total errors than the Low LA group on the 4-span length only, $F(1, 63) = 9.38$, $p = 0.003$ (Fig. 2).

Table 3
Backward Digit Task performance

	Low LA, M (S.D.)	High LA, M (S.D.)
Percent correct ANY-ORDER	93.09 (5.6)	90.11 (6.3)
Percent correct SERIAL-ORDER**	77.95 (13.2)	64.06 (14.5)
3-span length**	92.42 (8.5)	82.14 (14.2)
4-span length**	78.86 (18.0)	59.70 (21.1)
5-span length*	62.58 (18.9)	50.35 (16.1)
Total errors	9.64 (5.6)	15.22 (6.5)
3-span length	0.94 (1.2)	1.75 (1.3)
4-span length**	2.67 (2.1)	5.68 (4.1)
5-span length	6.14 (3.1)	7.81 (2.3)

*$p < 0.05$; **$p < 0.005$.

2.5. Qualitative error analyses for 4-span length

Given that perseveration and capture errors did not comply with tests of normality, the non-parametric Mann–Whitney U-test for between-group differences was employed for these 4-span length qualitative errors (Table 4). There was no significant difference between groups for perseverative errors ($p = 0.59$) however, the analysis for 4-span capture errors revealed a significant difference between LA groups ($U = 343$, $p = 0.008$) with the High LA group producing more capture errors than the Low LA group. Separate Mann–Whitney U tests on the specific errors types comprising the total capture error score, i.e., 4-span within-capture and 4-span between-capture errors, revealed that the High LA group produced significantly more within-capture errors only ($U = 333$, $p = 0.005$).

2.6. Regression analyses

Composite neuropsychological z-scores were calculated for executive functioning, language and memory. These composite indices and MMSE scores were included as predictor variables in separate stepwise regression analyses with percent correct in ANY-ORDER and percent correct in SERIAL-ORDER as the dependent variables. As detailed in Table 5, the final

Table 4
Qualitative error types for 4-span trial length

	Low LA, M (S.D.)	High LA, M (S.D.)
Total capture errors*		
4-Span length	1.29 (1.2)	2.34 (1.7)
Within-trial capture*		
4-Span length	0.79 (0.9)	1.75 (1.5)
Between trial capture		
4-Span length	0.50 (0.7)	0.59 (0.7)
Total perseverations errors		
4-Span length	0.29 (0.6)	0.59 (1.6)

* $p < 0.005$.

Table 5
Stepwise regression models

Step	Percent correct ANY-ORDER					Percent correct SERIAL-ORDER				
	Variable	R^2	Increment in R^2	R^2 change		Variable	R^2	Increment in R^2	R^2 change	
				F	p				F	p
Force	MMSE		0.172	8.09	0.007	MMSE		0.119	5.26	0.03
1	n.s.					Executive	z 0.288	0.169	9.04	0.005

regression model for ANY-ORDER accounted for 17.2% of the variance while the final regression model for SERIAL-ORDER accounted for 28.8% of the variance. Forcing MMSE into the equation at the initial step accounted for the entire 17.2% of ANY-ORDER performance variance but only 11.9% of SERIAL-ORDER performance variance. Subsequent stepwise procedures for the three composite z-scores resulted in no additional inclusions for the ANY-ORDER regression model while the executive composite z-score weighted by AcI, FAS and Clock accounted for an additional 16.9% of the SERIAL-ORDER performance variance.

2.7. Partial correlation analyses

One-tailed Partial Pearson's Product Moment Correlations were run for the 40-point Junque scale and ANY-ORDER as well as SERIAL-ORDER percent correct scores associated with the BDT covarying for MMSE. These analyses revealed a significant negative correlation only between the total Junque score and SERIAL-ORDER performance ($r = -0.362$, $p = 0.005$). This linear relationship (Fig. 3) held across all span lengths (3-span SERIAL-ORDER: $r = -0.292$, $p = 0.02$; 4-span SERIAL-ORDER: $r = -0.351$, $p = 0.007$; 5-span SERIAL-ORDER: $r = -0.276$, $p = 0.02$).

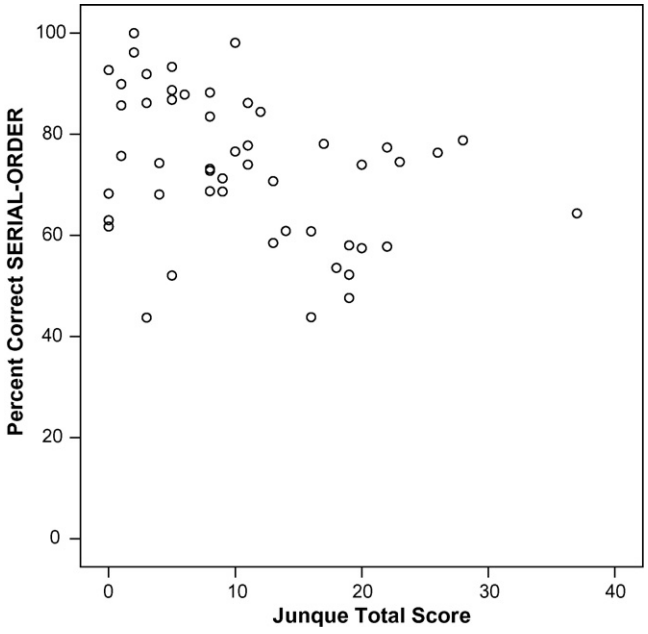

Fig. 3. Scatter plot of Junque total score against SERIAL-ORDER performance.

One-tailed partial correlations between the total Junque score and composite indices created from an average of normative based z-scores for executive functioning, language and memory were also conducted partialling out MMSE. These correlations revealed a significant negative relationship for total Junque score and the executive functioning composite index ($r = -0.45$, $p = 0.003$) as well as a significant positive association between the severity of LA and memory ($r = 0.62$, $p < 0.001$).

3. Discussion

The purpose of this study was to elucidate the relationship between LA and specific components of working memory in dementia. Our strategy was to combine a direct measure of LA with a digits backward paradigm to assess whether the severity of LA resulted in different types of working memory dysfunction. Results revealed that individuals with a high degree of LA, i.e., LA involving approximately 44% or more of white matter, had more difficulty than their Low LA counterparts when attempting to recall digits in reverse serial order despite no differential impairment in recalling the same digits in any order. These results suggest that a high degree of LA does not differentially interfere with less complex working memory storage and immediate (digit) recall abilities, but does interfere with higher-level working memory mental manipulation in the form of impaired disengagement and temporal re-ordering.

In addition to testing backward digit span, we assessed other cognitive and executive functions to provide additional support for our assertion that serial order digit recall involved higher-level executive functions. Of the variables used in the regression analyses, the composite executive function index of mental manipulation, spontaneous flexibility and working memory shown to require dorsolateral prefrontal regions for successful performance (Gourovitch et al., 2000; Mummery et al., 1996; Wildgruber et al., 1999) entered to explain SERIAL-ORDER digit recall but not ANY-ORDER digit recall. Although the variance for which these variables accounted was small, suggesting other aspects of cognition at play not represented in the current analysis, these results highlight the importance of these higher-level aspects of executive functioning to successful SERIAL-ORDER performance and provide additional information regarding the type of working memory dysfunction seen with higher levels of LA. The results of the regression analyses also suggest that while ANY-ORDER and SERIAL-ORDER error variables were derived from the same trials using the same BDT instructions, they appear to represent distinct aspects of executive dysfunction and the working memory process.

The participants with greater LA also produced more 'capture' errors, that is, a unique qualitative recall error involving the grouping of contiguous numbers in normal serial order (e.g., 16579 – '95671' or '96751'). This result suggests that High LA participants' impaired mental manipulation within working memory may be due, in part, to being unable to disengage from or inhibit over-learned and automatic procedural memories (Lamar et al., 1997; Stuss et al., 1995). Across several neuropsychological tests, the production of capture errors has been associated with a combination of higher order executive dysfunction as well as lower level disinhibition of more automatic behaviors (Giovannetti et al., 2001; Lamar et al., 1997). Furthermore, across a variety of paradigms, capture errors have been associated with frontal lobe damage (Della Malva, Stuss, D'Alton, & Willmer, 1993; Reverberi, Lavaroni, Gigli, Skrap, & Shallice, 2005). Initial results of individual types of capture errors suggest that the majority of the capture errors occurred within trial as opposed to between trials. This may suggest that individuals with greater LA had the capacity to deactivate previously activated digit representations and thus not perseverate across trials but lacked the ability to inhibit automatic or procedural memories that appeared with high saliency within trials. Until we can substantiate this interpretation using equal proportions of trials with and without contiguous numbers interspersed, any interpretation of the specific impact of LA on within or between trial capture types remains speculative. Only the High LA group, however, appeared vulnerable to both higher-level mental manipulation deficits as well as the disinhibition of automatized behavioral responses across the BDT.

The selective vulnerability to higher-level mental manipulation as well as disinhibition of automatized behavior in individuals with greater LA severity is further supported by the apparent double dissociation seen when investigating the relationship between Junque scores and composite *z*-scores. Much like our previous work (Price et al., 2005), the correlational analyses revealed a negative association between executive functions and LA severity and a positive association between verbal declarative memory and LA severity. This would suggest that LA severity selectively impairs working memory and executive function while sparing functions such as recognition memory and delayed recall. A closer look at the variables comprising the verbal declarative memory composite *z*-score reveals that the association is driven by the relationship between recognition memory and LA severity. Recognition memory is a less complex form of memory retrieval associated in part with the frontal lobes (Cabeza et al., 1997). It follows that these results are in keeping with our assertion that higher degrees of LA do not differentially interfere with less complex working memory and executive functions, but does interfere with higher-level working memory, mental manipulation and spontaneous flexibility.

According to Baddeley's model of working memory (Baddeley, Logie, Bressi, Della Sala, & Spinnler, 1986), the brain has lower level modality specific buffer systems that store and rehearse information and a higher-level central executive responsible both for overseeing these systems and executing processes like the manipulation and inhibition of information (Baddeley & Hitch, 1994). Immediate recall of the digits comprising the WAIS-R Digit Span Forward subtest purportedly demonstrates the integrity of storage and/or rehearsal skills (Collette, Van der Linden, Bechet, & Salmon, 1999; Hester, Kinsella, & Ong, 2004) and is mediated, in part, by Wernicke's (left hemisphere) perisylvian arc that includes the posterior superior portion of the temporal lobe, the supramarginal gyrus-arcuate fasciculus area of the parietal lobe and the inferior frontal lobe (Broca's area) (Heilman, Scholes, & Watson, 1976; Paulesu et al., 1993; Smith et al., 1998; Todd & Marois, 2004). In the current study, calculating the recall of BDT digits in any order allowed for the preservation of executive demand through the nature of the BDT instructions while simultaneously teasing out less complex aspects of working memory described above including storage and/or rehearsal skills. In contrast, recalling BDT digits in serial order requires disengaging from the presentation order represented in these short-term working memory stores and inhibiting previously acquired automatic behaviors as well as manipulating the information contained in these stores through temporal re-ordering. It is primarily these latter processes that are thought to be heavily dependent on the normal functioning of the higher-level central executive (Hester et al., 2004) as well as normal functioning white matter connections (Charlton et al., 2006) associated with the dorsolateral prefrontal cortex (Collette et al., 1999; D'Esposito et al., 1998) and which were most negatively impacted by increasing levels of LA in dementia.

In addition to these cortical areas of association to Baddeley's model of working memory, the basal ganglia (e.g., the caudate) and thalamus (e.g., dorsomedial) participate in the networks of cortical-striato-thalamo-cortical loops that interact with the dorsolateral frontal lobe. For example, the caudate also shows sustained activity during a memory delay in a working memory paradigm (Kawagoe, Takikawa, & Hikosaka, 1998). In addition, a functional imaging study has revealed that when mental manipulation of the material stored in working memory is required the caudate nucleus shows heightened activity (Lewis, Dove, Robbins, Barker, & Owen, 2004). Given that the posterior sensory systems that project to the frontal lobe do not have the ability to sustain persistent activity, these frontal-basal ganglia-thalamic-frontal loops might allow action potentials to be propagated to synaptic targets that in turn, are propagated to the originating cortical network. This reverberation might allow short-term persistence of memories (Constantinidis & Procyk, 2004) while data are manipulated by the frontal cortex.

The results of this study suggest that LA and associated white matter alterations disrupt and possibly disconnect reciprocal connections between cortical–subcortical as well as cortical–cortical white matter tracts (Merino & Hachinski, 2000; Mori, 2002; O'Sullivan et al., 2002; Price et al., 2005) (e.g., the cortical-striato-thalamo-cortical loops that interact with the dorsolateral frontal lobe) and that these disconnections may disrupt components of working memory associated with the higher-level central executive. Thus, these findings continue to support our theoretical assertion that direct frontal lobe damage is not necessary for various types of executive and working memory dysfunction in dementia. Future research should be conducted assessing the impact of LA location and the extent of

involvement in regions connecting various aspects of cortex on specific types of executive and working memory dysfunction. The current research would suggest that connections involving the dorsolateral prefrontal cortices are most negatively impacted by LA in dementia, however, without precise LA localization this cannot be substantiated with the current data set. Initial work using diffusion tensor imaging (DTI) would suggest that working memory may involve a complex network of connections encompassing both anterior prefrontal regions and more posterior regions including the hippocampal complex and the caudate nucleus (Charlton et al., 2006; O'Sullivan, Barrick, Morris, Clark, & Markus, 2005); each of which has direct connections to the dorsolateral prefrontal cortices (see Goldman-Rakic, 1987 for review).

In focusing on the severity of LA regardless of dementia diagnosis we may be seen as not considering the impact of the specific disease neuropathology associated with our patients' clinical diagnoses of dementia. We would argue against this given that, as previously stated, empirical evidence is mounting regarding the increasing overlap of AD and VaD across neuropathological and clinical boundaries. Although LA is often considered a form of VaD induced by small vessel disease associated with the deposition of amyloid or lipohylanosis, concentrations of a-beta 40 and 42, previously associated with AD, have been associated with periventricular and deep white matter alterations (Gurol et al., 2006). Furthermore, there is evidence that amyloid might induce oligodentrocyte dysfunction and death (Lee et al., 2004). Reduced choline acetyltransferase activity, also associated with AD, has been shown deficient in the basal forebrain of individuals with VaD (Rossor et al., 1982). Moreover, recent DTI work investigating the impact of white matter damage on working memory suggests that decreases in working memory are associated with decreases in the integrity of white matter pathways across anterior, middle *and* posterior regions of interest within the centrum semiovale (Charlton et al., 2006). Parallel investigations incorporating diagnostic class into work exploring the role of LA severity on cognitive functioning may further clarify this issue.

When evaluating any study with a number of analyses and follow-up analyses, one must consider the possibility of type I error production. The probability of a type I error is of most concern for significant levels that hover close to 0.05; thus, the likelihood of type I errors decreases with decreasing *p*-values. It should be noted that the majority of our significant results were at *p*-values less than or equal to 0.005.

Relying on levels of white matter alteration and measures of MRI LA burden is professed to yield more fundamental observations regarding the interplay between leukoaraiosis and the behavioral manifestations of dementia (Bowler & Hachinski, 1995; Bowler, Steenhuis, & Hachinski, 1999; Schneider et al., 2003). Determining patient groups based on LA is a step toward increasing our understanding of the impact white matter alterations may have on specific aspects of cognitive functioning. The concept of LA burden does not seek to replace the commonly used diagnostic criteria for dementia. Rather, we believe the variable of LA can be used to promote the notion of a cascade of neuropathological events within white matter that is associated with dementia regardless of diagnosis and negatively impacts the neural networks involved in higher cognitive and executive functions.

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