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Note

The impact of region-specific leukoaraiosis on working memory deficits in dementia

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ABSTRACT

MRI leukoaraiosis (LA) is less likely to interfere with simple compared to more complex working memory (WM) skills. We hypothesize that LA within the left hemisphere negatively impacts higher-level WM processes in dementia. Participants with dementia ($n = 64$; MMSE = 22.0 ± 3.4) performed a Backward Digit Task measuring simple storage/rehearsal (ANY-ORDER) and complex disengagement/temporal re-ordering (SERIAL-ORDER) recall. A visual rating scale categorized MRI-LA in five regions per hemisphere: frontal and parietal centrum semiovale, white matter around the frontal horns, body of the lateral ventricles and posterior horns. Amidst equivalent hemispheric LA scores [$t(62) = -1.12$, $p > 0.05$], correlations revealed an association between left-sided LA and SERIAL-ORDER recall ($r = -0.31$, $p = 0.007$) with LA around the posterior horn ($\rho = -0.30$, $p = 0.008$) and frontal centrum semiovale ($\rho = -0.29$, $p = 0.01$) showing the greatest association. Regression modeling confirmed the left posterior horn contribution to SERIAL-ORDER performance variance. Results suggest involvement of anterior (fronto-striatal) and more posterior (inferior parietal) white matter tracts in higher order WM deficits in dementia.

1. Introduction

Magnetic resonance imaging (MRI) evidence of leukoaraiosis (LA) is often associated with vascular disease and dementia (Hachinski, Potter, & Merskey, 1987). Regardless of dementia subtype, the presence of LA is associated with impairments in cognition functions mediated by the frontal lobes including executive functions (e.g., Lamar et al., 2007; Price, Jefferson, Merino, Heilman, & Libon, 2005; Skoog, Berg, Johansson, Palmertz, & Andreasson, 1996). More specifically, increasing LA in dementia, independent of clinical diagnosis, is associated with impaired disengagement and temporal re-ordering (Lamar et al., 2007); executive skills critical for the mental rearrangement of information held in working memory (WM). While several neuroimaging studies have outlined the neuroanatomical underpinnings of distinct components of WM (D'Esposito et al., 1998; Paulesu, Frith, & Frackowiak, 1993; Smith, Jonides, Marshuetz, & Koeppe, 1998), only those related to higher order executive abilities such as disengagement and temporal re-ordering were attributed to the prefrontal cortex. These higher-level WM abilities have been shown historically to be mediated, in part, by the frontal lobes (Jacobsen, 1936) and the left frontal lobe is particularly important for temporal ordering (Fuster & Alexander, 1971). In a previous paper (Lamar et al., 2007), we proposed that LA induced white matter disconnections of the left hemisphere, and more specifically the left anterior (prefrontal) regions, would impair higher-level WM processes in dementia.

Studies report an association between frontal LA and executive dysfunction in Alzheimer's disease (AD). Frontal LA correlated with measures of mental switching and maintaining set in AD (Gootjes et al., 2004). Furthermore, periventricular LA, while present in both normal aging and AD was found to correlate with higher-level WM processes only in the AD group (Burns et al., 2005). Left frontal periventricular LA accounted for deficits in cognitive initiation and mental set in individuals diagnosed with or at risk for AD (Fernaeus et al., 2001). While these studies support a possible role for left

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anterior (prefrontal) LA in executive dysfunction in dementia, the presence of neuronal degeneration primarily induced by AD limits the ability to generalize this finding to other forms of dementia. Furthermore, given that executive functioning encompasses many cognitive skills, the influence of LA burden on any one skill, particularly aspects of WM, is difficult to discern from the literature.

Our previous study, reported in this journal, investigating WM deficits associated with LA in patients with dementia found subtle differences in this executive skill that appeared independent of dementia subtype. Specifically, LA did not interfere with less complex WM storage and rehearsal but did impair higher-level WM mental manipulations requiring disengagement and temporal reordering (Lamar et al., 2007). While this prior study detailed the relationship between LA and specific aspects of WM, it only hypothesized about how the anatomic locus of LA might influence these results. Thus, studies evaluating the impact of region-specific LA on aspects of WM independent of dementia subtype are warranted. This report combines region-specific measures of LA (rs-LA) and indices distinguishing aspects of WM in dementia to provide preliminary data in support of the hypothesis that left hemisphere LA negatively impacts higher-level relative to less complex WM processes in dementia through a prefrontal disconnection involving anterior white matter regions.

2. Methods

2.1. Participants

The subjects in this study were recruited from a university affiliated outpatient memory clinic and were examined by a social worker, neurologist and neuropsychologist. Individuals were diagnosed as having dementia, either NINCDS-ADRDA probable AD (McKhann et al., 1984), probable/possible vascular dementia (VaD) using the California Criteria of Chui (Chui et al., 1992) or mixed AD/VaD, by interdisciplinary team conference. Patients administered the Backward Digit Task (BDT; Lamar et al., 2007) were eligible for inclusion. Exclusionary criteria included MRI evidence of cortical infarctions or lacunes, a history of head injury, substance abuse, major psychiatric disorders including major depression, epilepsy, B12, folate, or thyroid deficiency. Sixty-four participants (age = 79.5 ± 5.6) with mild to moderate dementia (MMSE = 22.0 ± 3.4) met study criteria (Table 1). IRB approval was obtained for this study with consent obtained according to the Declaration of Helsinki.

2.2. Apparatus and procedures

The BDT, described in detail elsewhere (Lamar et al., 2007), assessed aspects of WM including storage and rehearsal versus disengagement and temporal reordering. The BDT consists of seven trials of 3-, 4- and 5-digit span lengths verbally presented by the examiner and repeated in reverse order by the participant. Standardized WAIS-III Digit Span Backward procedures were followed except for the discontinuation rule; participants received all 21 trials regardless of performance. The dependent variable, percent correct in SERIAL-ORDER has been shown to rely on accurate serial position recall reflecting higher-level WM mental manipulations of disengagement and temporal re-ordering (Lamar et al., 2007). In contrast, the dependent variable percent correct in ANY-ORDER relies on recall of presented digits regardless of serial placement reflecting less complex WM and attentional skills involving immediate storage and rehearsal (Lamar et al., 2007). These two dependent variables, used in subsequent analyses, were calculated using the algorithm: [(total # correct)/(total possible correct)] × 100.

A 1.5 Tesla Siemens MRI scanner acquired T1-weighted (TR-500 ms, TE-9 ms) and FLAIR (TR-8500 ms, TE-99 ms) images of 5 mm thickness and 1 mm gap. Board-certified neuroradiologists (JB & SS) blinded to clinical and diagnostic data graded white matter using the 40-point Leukoaraiosis Scale of Junque (Junque et al., 1990). This MRI visual rating scale categorizes MRI-LA into five regions per hemisphere (Fig. 1a): frontal centrum semiovale, parietal centrum semiovale, white matter around the anterior frontal horns, white matter around the body of the lateral ventricles and white matter around the posterior horns (originally termed the atrium/occipital horn; Junque et al., 1990). Each region was graded separately (i.e., overlap was not considered) with scores ranging from 0-no visible LA to 4-severe LA and summed per region (range = 0–4) as well as per hemisphere (range = 0–20; Fig. 1b). Interrater reliability for the Junque scale was quite high ($r = 0.93$, $p < 0.001$).

The Junque scale is a semi-quantitative measure of white matter with composite hemispheric LA scores (right/left) meeting criteria for normality; thus, parametric testing was used for all analyses concerning the right and left hemisphere LA scores. Scores for each of the five regions, however, are not strictly interval data and thus are cruder measures that did not meet criteria for normality based on the Kolmogorov–Smirnov statistic. Therefore, non-parametric procedures were employed for all analyses concerning the rs-LA variables. To correct for multiple comparisons, significance for all analyses was $p < 0.01$.

3. Results

Within the context of equivalent hemispheric LA scores [right = 4.9(3.8), left = 5.1(4.0); $t(62) = -1.12$, $p > 0.05$], one-tailed Pearson correlations between BDT variables and right and left LA revealed an association between left-sided LA and SERIAL-ORDER recall only ($r = -0.31$, $p = 0.007$). Neither BDT variable correlated with right-sided LA (Table 2). Furthermore, correlation coefficients between right-sided LA and BDT variables were significantly smaller than those between left-sided LA and BDT variables, i.e., *r*-value comparisons for SERIAL-ORDER: $t(60) = 10.6$, $p < 0.001$; ANY-ORDER: $t(61) = 11.8$, $p < 0.001$. These results remained unchanged after controlling for the individual influence of age, education

Table 1
Participant characteristics and BDT performance

	M ± S.D.	Range
N	64	
Age (years)	79.5 ± 5.6	65–90
Education (years)	12.4 ± 2.2	6–12
MMSE	21.9 ± 3.4	13–28
GDS	3.7 ± 3.5	0–12
Junque score		
Right-sided	4.9 ± 3.8	0–20
Left-sided	5.3 ± 4.0	0–20
Sex (M:F)	14:50	
Diagnosis (AD:VaD:Mix)	29:23:12	
BDT recall (%)		
SERIAL-ORDER	72.2 ± 14.5	33–100
ANY-ORDER	92.3 ± 5.5	77–100

Note: M ± S.D.: mean ± standard deviation; MMSE: Mini-Mental State Examination; GDS: Geriatric Depression Scale; AD: Alzheimer's disease; VaD: vascular dementia; Mix: AD/VaD; BDT: Backward Digit Task.

Table 2
Correlations of hemisphere (parametric) and regional (non-parametric) leukoaraiosis measures to ANY-ORDER and SERIAL-ORDER working memory variables

	ANY-ORDER *r*-value	SERIAL-ORDER *r*-value
LA by hemisphere		
Left-sided	−0.13	**−0.31**
Right-sided	−0.05	−0.26
LA by region		
Frontal centrum semiovale		
Left	−0.21	**−0.29**
Right	*−0.07*	*−0.16*
Parietal centrum semiovale		
Left	−0.13	−0.23
Right	*−0.02*	*−0.18*
White matter around the anterior frontal horns		
Left	−0.02	−0.15
Right	*−0.04*	*−0.17*
White matter around the body of the lateral ventricles		
Left	−0.08	−0.18
Right	*0.01*	*−0.12*
White matter around the posterior horns		
Left	−0.28	**−0.30**
Right	*−0.23*	*−0.25*

Note: LA: leukoaraiosis; bolded values highlight significant results after correcting for multiple comparisons ($p < 0.01$); italicized values denote that the overall right-sided LA score did not correlate to ANY- or SERIAL-ORDER performance.

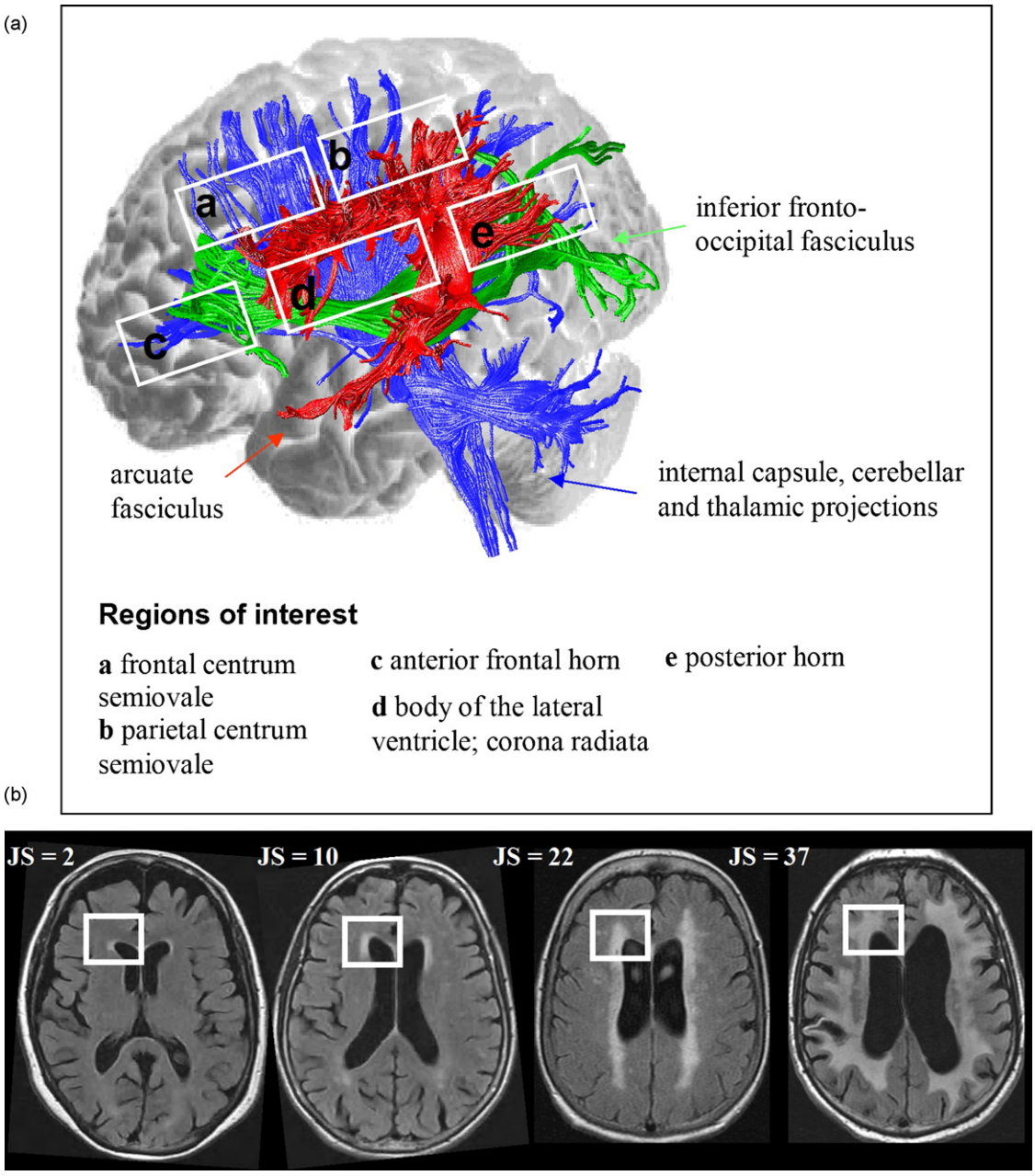

Fig. 1. (a) Regional divisions of the 40-point Leukoaraiosis Scale of Junque (JS) illustrated on a tractography reconstruction of white matter tracts passing through the left hemisphere (tracts derived from Catani et al., 2002; mod.); (b) examples of the degree of MRI-LA severity according to the 40-point JS highlighting the left anterior frontal horn.

and sex; controlling for MMSE attenuated results but the pattern of significance remained unchanged (i.e., left-sided LA and SERIAL-ORDER recall only; $r = -0.29$, $p = 0.01$). Separate Spearman's ρ correlations (one-tailed) for the five left-sided rs-LA measures revealed that LA around the left frontal centrum semiovale ($\rho = -0.29$, $p = 0.01$) and left posterior horn ($\rho = -0.30$, $p = 0.008$) negatively correlated with SERIAL-ORDER recall.

Given that the rs-LA measures did not meet criteria for normality, these measures were logarithmically transformed (adding 1 to each individual index to avoid sum scores of zero) before inclusion as predictor variables in separate regression analyses with BDT variables as dependent measures. The SERIAL-ORDER regression model accounted for 23.2% of performance variance. The forced entry of MMSE scores in the first step to control for general declines in cognition accounted for 15.7% of performance variance (standardized beta coefficient = 0.37, $p = 0.002$) while left posterior horn LA accounted for 7.4% of performance variance, a significant contribution in the second stepwise step involving the five left hemisphere rs-LA scores (standardized beta coefficient = −0.27, $p = 0.01$). Only MMSE contributed to the ANY-ORDER model explaining 8.1% of performance variance (standardized beta coefficient = 0.28, $p = 0.02$). Forcing age not MMSE into the first step, given the assumption that increasing age is associated with increasing LA, did not account for any variance in the SERIAL-ORDER model and only 0.3% in the ANY-ORDER model. Left posterior horn LA, however, continued to contribute to SERIAL-ORDER recall performance variance only, r^2 change = 9.8% and standardized beta coefficient = −0.31, $p = 0.01$.

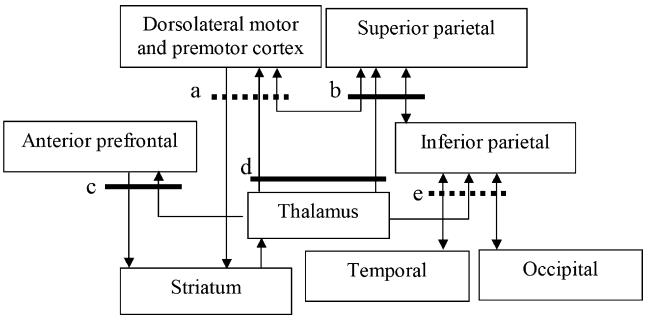

Fig. 2. Representation of the fiber bundles connecting cortical and subcortical regions of brain (a–e) with hypothesized disconnections resulting from LA within the frontal centrum semiovale (a) and posterior horn (e).

4. Conclusions

These preliminary data support the postulate that, when considering the executive skill of WM, LA location influences the type of deficits associated with dementia. Left-sided LA appeared more detrimental to higher-level when compared to less complex WM functions than right-sided LA. Within the left hemisphere, higher-level WM mental manipulations of disengagement and temporal re-ordering were disrupted in the presence of frontal centrum semiovale LA but not LA in the anterior (frontal) horn. This relative distinction may suggest region-specificity within the frontal lobe as it relates to specific WM deficits in dementia. The frontal centrum semiovale contains connections from the dorsolateral prefrontal cortex to the striatum and feedback projections from the thalamus to the frontal lobes (Catani, Howard, Pajevic, & Jones, 2002; Fig. 1a). Thus, the impairment on our task appears to be related, in part, to disruption of the fronto-striatal and/or thalamo-frontal loop in the left hemisphere (Fig. 2); an assertion supported by neuroimaging work in WM (e.g., Charlton et al., 2006; Tsukiura et al., 2001) and large-scale epidemiological studies (de Groot et al., 2000, 2002). The frontal centrum semiovale also contains the arcuate and longitudinal fasciculi that may correspond to the additional association of left-sided LA within the posterior horn and the sequential rearrangement of material held in WM required by the BDT.

Orderly number sequencing and spatial processing rely on the integrity of a bidirectional network involving the parietal cortex (Hubbard, Piazza, Pinel, & Dehaene, 2005); additionally, previous work with backward digit processing suggests that visuospatial imagery is a useful strategy to facilitate performance (Hoshi et al., 2000). It is possible that the disengagement and temporal re-ordering of verbally presented digits is facilitated by mental number visualization and spatial manipulation. These skills involve a network encompassing the inferior parietal and occipito-temporal regions (Hubbard et al., 2005); a network that surrounds the posterior horn (e.g., through the arcuate fasciculi). Although this is only one possible explanation for the posterior (inferior parietal) LA involvement in impaired SERIAL-ORDER recall, previous studies support the role of posterior parietal regions in WM mental manipulation (Collette et al., 2001). Additionally, multiple studies advocate the impact of disruption to long association fibers connecting prefrontal to subcortical as well as more distant brain regions on rates of cognitive decline and dementia (Charlton et al., 2007).

Given there are several white matter pathways that traverse the injured white matter regions within the left frontal centrum semiovale and posterior horn (Catani, Jones, Donato, & Ffytche, 2003) highlighted in this study, we cannot specifically determine the white matter tracts that, when disrupted, induce the higher-level WM dysfunction in dementia. We would hypothesize, however that a disruption exists within the fronto-striatal loop coupled with a posterior inferior parietal network of disconnectivity (Fig. 2) negatively impacting BDT performance in our dementia population. Previous investigations have identified distinct topographies of impaired white matter as they relates to executive dysfunction. Some highlight the role of lacunar infarctions and white matter hyperintensities in the basal ganglia in disrupting and possibly disconnecting the fronto-striatal loop (Grau-Olivares, Arboix, Bartres-Fez, & Junque, 2007; Grau-Olivares, Bartres-Faz, et al., 2007; O'Brien et al., 2002) while others point to the inclusion of more posterior regions of involvement when determining the influence of white matter damage on executive dysfunction (Jokinen et al., 2005). Our study attempts to combine both anterior and posterior regions of white matter damage in a detailed explanation of the specific WM deficits in disengagement and temporal re-ordering seen after LA accumulation in dementia.

Although it could be argued that our results might provide different information if we studied patients with one form of dementia (e.g., VaD) versus another (e.g., AD), increasingly, studies show similar LA involvement throughout brain independent of dementia diagnosis (Gootjes et al., 2004). This suggests that the WM deficit seen in our dementia population is most likely induced by LA rather than LA associated with any particular dementia subtype. It could also be argued that lacking a healthy control comparison group, it is difficult to state with certainty if our results are specific to LA in dementia or a result of LA in aging. Controlling for age in our correlational analyses did not impact our results nor did its inclusion in our regression analyses account for any variance in BDT performance; it did, however, allow for greater variance to be explained by left-sided posterior horn LA than that seen with the inclusion of overall cognitive status. Region-specificity and executive dysfunction has been demonstrated in patients with ischemic LA (O'Sullivan et al., 2004) and those with AD (Burns et al., 2005) when compared to healthy controls despite the presence of LA across these aging populations. In the current study, statistical differences between correlations for left- and right-sided LA further support the region-specificity of left-sided LA results in dementia as opposed to the mere presence of LA in the aging brain given that LA is thought to be present in equal proportions across hemispheres (Gootjes et al., 2004) and have a synergistic impact on dementia pathogenesis (Jellinger, 2002; Luchsinger et al., 2005).

Neuroimaging advances like diffusion tensor MRI (DT-MRI) allow for quantification of disruption of white matter integrity within specific tracts. This might allow investigators to obtain a more complete picture of the relationship of LA to specific white matter pathways and the role of injury to these pathways on WM functions. Emerging (Charlton et al., 2007) and future studies using DT-MRI to assess the relationship between LA and specific aspects of WM deficits in dementia and healthy aging might help to verify and expand our preliminary results. Furthermore, a larger-scale study involving a wider variety of neuropsychological test measures (e.g., a spatial variant of our WM task that might reveal greater right hemisphere involvement) would assist in the determination of the contribution of region-specific LA to higher-level WM functions as opposed to other types of executive and/or cognitive skills.

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