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Linking MRI Hyperintensities With Patterns of Neuropsychological Impairment

Evidence for a Threshold Effect

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Background and Purpose—Leukoaraiosis (LA) might interrupt intra- and interhemispheric communication and thus induce cognitive impairments and dementia. It remains unclear, however, if there is a volume threshold of LA that is needed before either the signs of dementia and/or a specific pattern of neuropsychological impairment become manifest. Roman et al has suggested that 25% of white matter may need to be involved before white matter alterations influence the clinical signs associated with dementia. The purpose of this study is to ascertain the threshold of MRI-LA as measured with a visual rating scale needed to induce specific patterns of neuropsychological impairment associated with dementia.

Methods—One hundred fifteen patients with dementia received a comprehensive neuropsychological examination and the severity of MRI-LA was measured using a 40-point LA scale.

Results—Patients were categorized into low (mean LA=4.21±2.92; 3.22%–17.82%), moderate (mean LA=12.58±2.54; 25.01%–37.80%), and severe (mean LA=22.36±4.04; 45.80%–66.00%) LA groups. Patients in the mild LA group obtained markedly lower scores on tests of episodic memory compared with working memory, a neuropsychological profile often associated with Alzheimer disease. Patients with moderate LA displayed equal impairment on neuropsychological tests. Patients in the severe LA group obtained significantly lower scores on tests of working memory as compared with episodic memory.

Conclusions—These data provide evidence that a threshold of moderate MRI-LA as measured with a visual rating scale is associated with greater and/or equal impairment on tests of working memory versus episodic memory and provides a benchmark to assess the effect of MRI-LA on the clinical presentation of dementia. **(*Stroke*. 2008;39:806-813.)**

Key Words: Alzheimer disease ■ Binswanger disease ■ episodic memory ■ executive functions ■ leukoaraiosis ■ subcortical dementia ■ vascular dementia

There is now keen interest in the relation between vascular disease and dementia.[1] However, it remains unclear how to correctly make the diagnosis of vascular dementia and/or to assess the neuropsychological manifestations of subcortical vascular disease in the clinical presentation of neurodegenerative dementias such as Alzheimer disease (AD). Unfortunately, comparatively little neuropathological research has been conducted correlating the neuropathological changes of white matter induced by vascular disease with neuropsychological impairments. Therefore, the specific brain–behavior relationships induced by vascular disease in patients with dementia remain largely unknown. Several prior neuropsychological studies performed with patients with dementia who had imaging evidence of white matter disease that was thought to be associated with small vessel disease and ischemia suggest an association between white matter alterations and impairments on tests of executive control (see Libon et al[2] for a review). Yet, the wide array of neuropsychological tests used in this body of research and the means by which these patients are diagnosed limit the external validity of this research.[2]

Many MRI studies obtained from nondemented older people also demonstrate evidence of white matter alterations on T2 or fluid-attenuated inversion recovery MRI. These alterations of the white matter have been called leukoaraiosis[3] (LA). The etiology of MRI white matter changes is not entirely known;

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however, LA is often thought to be induced by small vessel disease associated with lipohyalinosis and amyloid angiopathy. Whatever their cause, LA might be a sign of a disruption of cortical–subcortical networks, which are understood to play a key role in modulating cognitive activities.

The degree of LA varies considerably across individuals; thus, it is possible that before clinical signs and symptoms associated with LA become manifest, the loss in this neuromodulatory system must reach a threshold. Observations of patients with Parkinson disease reveal that people might lose up to 60% to 70% of their dopaminergic neurons and remain asymptomatic. However, when 80% to 90% of dopaminergic neurons are lost, patients with Parkinson disease become symptomatic.[4] Because some people who manifest MRI-LA have no signs or symptoms of dementia, it has been posited that a sufficient volume of cortical–subcortical connections must be interrupted before neurobehavioral signs and symptoms become manifest.[1] Price et al[5] found some support for this hypothesis in a retrospective analysis of the relationship between MRI-LA and performance on tests of executive control and episodic memory.

The purpose of this article is to prospectively test the notion that it is possible to associate a specific threshold of MRI-LA with specific patterns of neuropsychological impairment. Therefore, in this research, we prospectively enrolled a new cohort of patients with mild dementia and performed quantitative measures of MRI-LA. As compared with other cortical regions, frontal lobe functions are particularly dependent on subcortical connections. Thus, we predicted that frontal/executive functioning would be more impaired than other cognitive functions in individuals with greater MRI-LA. In our prior research,[5] we provided support for this hypothesis. In the current study, we tested the hypothesis that a threshold of MRI-LA would induce a specific pattern of impairment on neuropsychological tests characterized by greater frontal system impairment with less impairment on tests that assess episodic memory and lexical access. If successful, this prospective research, coupled with the results from our previous study, would provide converging support for the postulate that a threshold of LA, as measured by MRI studies, can be associated with specific patterns of impairment on neuropsychological tests. This threshold method might also provide a basis for identifying when MRI-LA is making a contribution to the clinical presentation of dementia.

Methods

Participants

A cohort of 115 new subjects with dementia was drawn from an outpatient memory clinic. This patient group is separate from the retrospective analysis reported by Price et al.[5] Using the criteria of McKhann et al[6] and Chui et al,[7] our sample consisted of 62 patients who met criteria for diagnosis of probable AD[6] and 53 patients who met criteria for the diagnosis of probable/possible ischemic vascular dementia (IVD).[7] Patents were diagnosed with AD or IVD on the basis of a consensus among a neuropsychologist, neurologist, and social worker. For the subsequent MRI analyses described subsequently, participants were treated as a single group and the between-group variable of interest in this article is the severity of MRI-LA.

Medical history was gathered from a knowledgeable family member. Brain MRI scans and diagnostic laboratory studies were obtained to evaluate for reversible causes of dementia. Exclusion criteria included MRI evidence of cortical infarctions, history of head injury, substance abuse, major psychiatric disorders, epilepsy, vitamin B12, folate, or thyroid deficiency as well as any chronic medical condition that could adversely influence cognition. Other exclusion criteria included a sudden onset of a cerebrovascular accident and/ or a stepwise decline in cognitive abilities. This research has been approved by the University of Medicine and Dentistry of New Jersey–School of Medicine Institutional Review Board.

MRI Analysis

A 1.5-Tesla Siemens MRI scanner was used to obtain T1-weighted (TR 500 ms, TE 9 ms) and fluid-attenuated inversion recovery (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.[8] This MRI visual rating scale is similar to several other scales.[9–11] We chose the Junque LA Scale because its range of measurement (ie, 0–40) permits statistically robust analyses.[5] In previous research, this MRI visual rating scale has been associated with specific cognitive deficits.[2,13]

A board-certified neuroradiologist, who was unaware of all clinical data as well as the dementia diagnosis, graded the presence and severity of LA in several specific areas of each hemisphere. These areas included: 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 occipital horns. LA scores for each area, in each hemisphere, ranging from 0 (no visible white matter alterations) to 4 (severe white matter alterations), were summed for a total LA Scale score (total maximum score=40).

MRI-LA Classification

To assess the effect of MRI-LA on neuropsychological functioning, LA scores were used to divide patients into low, moderate, and severe LA groups. A frequency distribution of our patients indicated that the LA scale ranged from 0 to 30. To assign patients into the mild, moderate, or severe MRI-LA groups, we divided the scale into 3 relatively equal portions. In the mild LA group, a mean of approximately 10% of the white matter was involved (LA=0 to 8; n=57); in the moderate LA group, approximately 31% of the white matter was involved (LA=9 to 17; n=36); and in the severe group, approximately 56% of the white matter was involved (LA=18 to 30; n=22). We acknowledge that the 40-point Junque LA, as well as any other MRI visual rating scale, is best viewed as a proxy of true white matter involvement. Thus, we acknowledge that there can be no direct quantitative association between percent of LA involvement as calculated using the Junque LA Scale with actual white matter disease that might be seen on autopsy. Still, preliminary research from our laboratory analyzing MRI-LA using Scion Image Beta 4.1, a public domain National Institutes of Aging Image pixel-processing program (developed at the US National Institutes of Health and available on the Internet at http://rsb.info.nih.gov/nih-image/), suggests that the Junque LA score and computer-assisted pixel measurement of brain white matter are highly correlated ($r=0.735$, $P<0.001$, n=56).

Neuropsychological Assessment

The neuropsychological protocol described subsequently was selected because the validity of these measures has been established.[2]

Working memory was assessed with the Boston Revision of the Wechsler Memory Scale–Mental Control subtest (WMS-MC).[13,14] In addition to the 3 tasks that comprise the standard WMS-MC (ie, counting from 20 to 1, reciting the alphabet, and adding serial 3's), the WMS-MC includes 4 additional tasks: reciting the months of the year forward and backward, identifying letters that rhyme with the word "key," and naming all letters that have curved lines when visualized as capital, block-printed letters (eg, B, C, D, and so on). Patients were allowed to work as long as necessary as long as they worked meaningfully. The dependent variable for this task was an

Table 1. Leukoaraiosis Scores and Demographic Information: Means and SDs

Group	LA Score	Age	Education	MMSE	WAIS-R Similarities	GDS
Mild LA	4.21 (2.92)	78.53 (5.78)	12.58 (2.71)	22.91 (2.75)	11.89 (5.73)	3.47 (2.98)
Moderate LA	12.58 (2.54)	80.78 (5.22)	12.31 (2.77)	22.28 (3.62)	10.22 (4.37)	3.83 (3.74)
Severe LA	22.36 (4.04)	78.73 (4.99)	11.91 (2.68)	21.68 (3.35)	11.09 (5.60)	4.64 (3.04)

MMSE indicates Mini-Mental State Examination; WAIS-R, Wechsler Adult Intelligence Scale–Revised; GDS, Geriatric Depression Scale.

accuracy index (AcI) derived from the 3 nonautomated tasks (ie, months backward, alphabet rhyming, and alphabet visualization). The accuracy indices for each nonautomatized task were based on the following algorithm: AcI=[1−(false-positive+misses/#possible correct)]*100. This algorithm yields a percentage score ranging from 0 to 100 (100% correct results in the correct identification of all targets with no misses or false-positive responses). A composite AcI score was calculated by averaging the AcI's from these subtests. Prior research has shown that performance on these tests is sensitive to the volume of LA in patients with mild dementia.[13] When similar tasks are performed by normal participants, the functional imaging technique has shown activation of the prefrontal cortex.[15]

Visuoconstruction ability was assessed by asking patients to draw a clock face, to verbal command, and to copy a clock face. Patients were asked to draw the hands to indicate the time of "10 after 11."[16] Following published procedures,[17] 10 errors related to graphomotor impairments, hand/number placement, and executive control were scored as either 1 (present) or 0 (absent) for both the drawing to command and copying conditions (range, 0 to 20 errors). The dependent variable derived from this test was the total number of errors summed across the drawing to command and copying tests.[17] Previous research with patients diagnosed clinically with AD, IVD, and subcortical dementia syndromes such as Parkinson disease and Huntington dementia has shown differential patterns of performance on this test.[12,18,19] Patients with IVD or a substantial degree of MRI-LA tend to make more executive errors such as perseverations than patients with AD.[12] Thus, the clock drawing test is thought to be a sensitive measure of frontal–subcortical dysfunction.

Lexical Fluency Index was assessed by using a ratio examining output for the "animal" category word list generation task and output for the letter "S" from the "FAS" Controlled Oral Word Association task.[20] In the category fluency test, patients were asked to name as many animals as possible during a 1-minute interval and in the letter–phoneme fluency task, the patients were asked to say as many words as possible during a 1-minute interval that start with the letter "S" but not to use proper names or derivatives of previously used words.[20] Imaging studies have shown that letter–phoneme fluency tests activate the left dorsolateral prefrontal region in younger[21] and older[22] adults. Recent studies have shown that performance on category fluency tests tends to activate the left temporal lobe.[22,23] For this study, a lexical access/fluency ratio was calculated based on the total number of "animal" responses divided by the sum of the number of animals named and the total number of word that start with "S" that were named (ie, [total animals responses/(total animals responses+total "S" responses]).[24] A higher ratio score indicates that participants generated more animal versus letter responses, suggesting relatively better temporal than frontal function and vice versa.

Episodic Memory was assessed with the Philadelphia (repeatable) Verbal Learning Test (PVLT).[25–27] The P(r)VLT is modeled after the California Verbal Learning Test and consists of a 9-word list drawn from 3 semantic categories administered over 5 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, the delayed recognition discrimination index was used. This index was chosen for several reasons. First, previous factor analytic studies with patients with dementia have shown that both the 9-word, experimental California Verbal Learning Test and the P(r)VLT produce 3 to 4 factor solutions with performance on free recall, the production of intrusion errors as well as performance on the delayed recognition test loading on separate factors.[25,28] Second, free recall test trials can be impaired for numerous reasons, including retrieval deficits. Thus, recognition test trials are considered a more "pure" measure of episodic memory encoding ability. In fact, Libon et al[30,31] has shown that greater atrophy of the parahippocampal gyrus is associated with a lower recognition discrimination test scores and that patients with AD obtain particularly low scores on the California Verbal Learning Test/P(r)VLT delayed recognition test relative to other dementia groups.[31] In sum, all of this research suggests that the P(r)VLT recognition discrimination subtest is an excellent measure of the encoding deficit often seen in dementia.

Results

Demographics

The groups did not differ in terms of age, education, severity of dementia (as assessed with the Mini-Mental State Examination),[32] or depression (as assessed with the Geriatric Depression Scale[33]). General intellectual functioning was assessed with the Wechsler Adult Intelligence Scale–Revised, Similarities subtest.[34] No between-group differences were found (Tables 1 and 2).

Regression Analysis

For this analysis, the MRI-LA score was the dependent variable and raw scores derived from the 4 neuropsychological measures described previously were the independent variables. Age, education, gender, and Mini-Mental State Examination scores were entered first. These variables accounted for only 5% of the variance ($r=0.237$, $R^2=0.056$, $F=1.63$, nonsignificant). Next, the 4 neuropsychological variables all entered and accounted for a total of 35% of the variance ($r=0.592$, $R^2=0.350$, $F=12.00$, $P<0.001$). However, only 2 of the 4 neuropsychological variables were significantly related to MRI-LA: the WMS Mental Control–AcI ($B=-0.266$, $t=2.65$, $P<0.009$) and the P(r)VLT Recognition Discrimination subtest ($B=0.303$, $t=3.27$, $P<0.001$).

Between-Group Multivariate Analysis of Variance

The effect of neuropsychological functioning on MRI-LA was assessed with a multivariate analysis of variance with MRI-LA group as the independent variable. The selection of dependent variables for this analysis was based on the outcome of the regression analysis described previously. Because only the WMS-Mental Control–AcI and the P(r)VLT Recognition Discrimination subtest were related to MRI-LA, only these 2 variables were included in the multivariate analysis of variance. This analysis yielded a significant multivariate effect for group ($F^{4,220}=11.02$, $P<0.001$), and both univariate analyses of variance were significant (WMS Mental Control–AcI, $F^{2,112}=12.83$, $P<0.001$; P(r)VLT Recognition Discrimination subtest, $F^{2,112}=15.33$, $P<0.001$).

Table 2. Neuropsychological Data: Means and SDs

	Mild LA	Moderate LA	Severe LA
WMS-AcI			
Raw score	76.42 (15.83)	60.65 (25.95)	52.52 (22.80)
z-score*	0.41 (0.69)	–0.27 (1.13)	–0.62 (0.99)
Clock drawing errors			
Raw score	3.80 (2.30)	4.52 (2.36)	5.77 (1.92)
z-score	0.25 (0.99)	–0.50 (0.99)	–0.57 (0.80)
Fluency test performance			
Letter fluency (FAS) (raw score)	25.36 (10.46)	20.88 (11.32)	15.72 (7.59)
"Animal" fluency (raw score)	9.82 (3.71)	9.06 (2.90)	9.41 (3.81)
Lexical access/fluency ratio			
Raw score	0.54 (0.10)	0.58 (0.12)	0.64 (0.10)
z-score	–0.27 (0.92)	0.06 (1.03)	0.60 (0.86)
P(r)VLT delayed recognition Discrimination subtest			
Raw score	67.23 (11.50)	75.99 (12.32)	82.73 (11.88)
z-score	–0.43 (0.86)	0.23 (0.93)	0.73 (0.89)

*Z scores were calculated from the grand means and SDs from the entire dementia group rather than a normal control group.

WMS-AcI indicates Wechsler Memory Scale Non-Automatized Accuracy Index.

Follow-up analyses (Tukey tests) indicated that the mild MRI-LA obtained a better score on the WMS–Mental Control test than the moderate ($P<0.002$) and severe ($P<0.001$) MRI-LA groups. There was no difference between the moderate and severe MRI-LA group. On the P(r)VLT Recognition Discrimination subtest, the severe MRI-LA group obtained a better score compared with the mild MRI-LA group ($P<0.001$). There was a marginal effect such that the severe MRI-LA group outperformed the moderate MRI-LA group ($P<0.090$). The moderate MRI-LA group obtained a better recognition test score compared with the low MRI-LA group ($P<0.002$).

Within-Group Comparisons

Differential performance on neuropsychological tests was assessed with pairwise *t* tests. As stated previously, only the WMS Mental Control–AcI and P(r)VLT Recognition Discrimination subtests were used for these analyses. The dependent variables for these 3 comparisons were z-scores based on the grand means and SDs from our patient sample rather than a normal control group. This procedure was used to ensure that the dependent variables were normally distributed. These analyses yielded a double dissociation. As predicted, patients in the mild MRI-LA group obtained a better score on the WMS Mental Control–AcI subtest compared with the P(r)VLT Recognition subtest ($P<0.001$). The opposite profile was obtained for the severe MRI-LA group such that these patients now performed better on the P(r)VLT Recognition subtest compared with the WMS Mental Control–AcI ($P<0.001$). The moderate MRI-LA group displayed equal impairment on these tests (Table 2; Figure).

Discussion

The data described previously, linking the severity of MRI-LA and the patterns of performance on neuropsychological tests provides further evidence that "disease of the white matter does matter." Consistent with our previous retrospective report,[5] the regression analysis showed a relationship between MRI-LA and neuropsychological measures of delayed recognition memory and working memory, even after age, education, and general dementia severity were

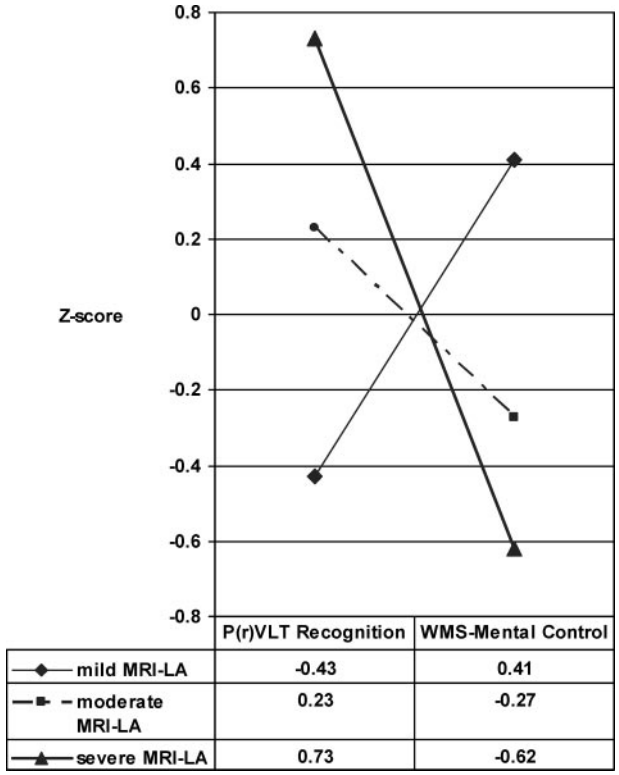

Figure. Episodic (PrVLT) and Working Memory Test (WMS-Mental Control–AcI) performance in patients with dementia with mild, moderate, and severe MRI-LA.

considered. Furthermore, within-group comparisons revealed a striking pattern such that a primary anterograde amnesia was associated with minimal to mild MRI-LA, whereas a dysexecutive syndrome was associated with severe MRI-LA. For patients with moderate MRI-LA, performance on both neuropsychological tests was equally impaired. We acknowledge the possibility that most, if not all, of our patients could very well qualify for a neuropathological diagnosis of AD. Nonetheless, we maintain that these data, in conjunction with our previous retrospective analysis,[5] provide converging evidence that a threshold of MRI-LA can be associated with differential impairment on neuropsychological tests whereby neuropsychological test performance may no longer be distinguished by severe primary anterograde amnesia and deficits involving lexical access, hallmark features of AD.

There is now a growing body of research suggesting that the relationship(s) among AD, vascular disease, and IVD are more complex than previously believed. For example, traditional risk factors for stroke have been linked with AD,[35–38] and vascular risk factors such as hyperhomocysteinemia, atherosclerosis, hyperlipidemia, hypercholesterolemia, and the presence of the APOE-4 or APOE-2 alleles are often seen in individuals with LA.[39–42] Also, as compared with clinic-based autopsy studies, population-based autopsy studies now suggest that the incidence of "pure" AD is often well below 50%.[43–45] Other research findings have shown that not all participants who meet pathological criteria for AD showed signs of cognitive impairment in life.[46,47] Even more intriguing is an emerging body of research suggesting that the neuropathology that underlies AD and IVD cannot only coexist, but may influence each other. A number of studies have demonstrated that AD neuropathology is sometimes less severe when accompanied by pathological evidence of vascular disease.[52] For example, data from the Honolulu–Asia Aging Study[52] found that patients with a marginal number of amyloid plaques had a substantial increase of dementia when concomitant vascular disease was present.

Chui and colleagues have published a series of papers that have examined the effect of AD and vascular pathology on neuropsychological functioning. Several important findings have emerged. First, MRI-derived measures of cortical and medial temporal lobe–hippocampal pathology are more robust predictors of cognitive impairment than MRI measures of white matter disease and lacunar infarcts.[51–54] Second, Chui et al[53] and Reed et al[54] have described a series of autopsy participants who were studied with detailed neuropsychological tests assessing executive control and episodic memory. In this research, postmortem AD pathology was associated with differential impairment on tests of episodic memory. By contrast, the association between pathological evidence of vascular disease and dysexecutive neuropsychological test performance was mixed and somewhat inconsistent. Chui et al[53] concluded that the effect of vascular disease on the clinical presentation of dementia was additive rather than synergistic. Reed et al[54] raised a serious caution about the usefulness of executive impairment as a marker for the diagnosis of IVD.

Our current study is quite similar to that of Reed et al[54] in several ways. First, rather than relying on clinical diagnosis as their major grouping variable, both studies have adopted a methodology whereby neuropsychological test performance is directly compared with a continuous measure of vascular disease. Second, both studies have reported a comparatively low incidence of patients presenting with striking evidence for a dysexecutive syndrome in association with severe vascular disease. In the present research, only 22 of 115 patients, or 19.13% of patients, presented with severe MRI-LA coupled with greater working memory versus episodic memory impairment. Third, both studies found that the majority of patients present with little vascular disease in association with a severe anterograde amnesia.

However, a significant point of divergence between our study and these former studies involves both the neuropsychological tests that were used and how neuropsychological test behavior is quantified. Libon and colleagues have generated a body of research showing that an effective way to measure the impact of MRI white matter alterations on cognition in patients with dementia is to examine the errors produced on neuropsychological tests in conjunction with correct responses.[12,13] Such an approach underlies the scores derived from the executive control measures used in the current research. There is also a significant difference in how both laboratories measure episodic memory. Reed et al[54] operationally defined episodic memory as the results of immediate free recall of trials 1 and 2 from a serial list learning test. By contrast, the operational definition of memory impairment in our prior[5] and current report was derived from a delayed recognition memory test. As stated previously, the rationale for using a delayed recognition memory measure is based on previous research demonstrating relative preservation on this kind type of test in patients whose dementia is associated with subcortical pathology versus AD. Moreover, the pattern of behavior that underlies 9-word California Verbal Learning Test and P(r)VLT recognition discrimination subtest scores is very striking. When patients are compared on the basis of either clinical diagnosis or MRI-LA severity, we have never observed any difference in the mean number of recognition correct hits. Rather, patient groups are distinguished on the basis of the number and distribution of their false-positive responses. Patients with significant MRI-LA make significantly fewer false-positive errors and their false-positive errors tend to be drawn from the interference test condition, suggesting a source recall problem.[28,31]

The results of the current research as compared with the findings reported by Chui et al[53] and Reed et al[54] underscore several very important methodological as well as theoretical issues, ie, what is the effect of both gray matter pathology and vascular disease on behavior and is autopsy data the final arbiter of the clinical presentation of dementia? Libon and colleagues have consistently shown that when frontal systems operations are assessed with timed or speeded measures, patients with significant MRI-LA not only produce differentially low scores, but their performance worsens over the time course of the task at hand. That is to say, from a statistical perspective, the performance of patients with dementia with significant MRI-LA is characterized by a negative slope.[13] The brain–behavior relationship(s) that underlie this phenomenon have yet to be elucidated. It is possible that in patients

with significant LA accompanied with neuropsychological evidence of dysexecutive functioning, LA may interrupt neurotransmitter–modulatory systems such as the catecholaminergic neurotransmitters and/or corticostraital and thalamocortical networks. Thus, it is possible that the typical autopsy protocols used in dementia research may not be able to capture the dynamics of such complex distributed neuronal networks. This might be an objective for future research.

The significance of the current research is 2-fold. First, the results of the current study replicate the findings from our previous report[5] and suggest that it may be possible to identify a threshold regarding when and how MRI-LA exercises a specific effect on the clinical presentation of dementia. Second, the validity of the findings described previously is supported by several corroborating lines of research. For example, preliminary evidence suggests that patients with dementia presenting with at least moderate MRI-LA sometimes respond better to medication such as donepezil.[55] Patients with dementia who at baseline presented with a Junque LA score of $\geq$10 demonstrated improvement on tests of working memory/executive control and on the P(r)VLT Delayed Recognition Discrimination subtest compared with patients who initially presented with minimal MRI-LA. Thomas et al[55] speculated that an initial clinical presentation involving at least moderate MRI-LA in association with evidence of a significant dysexecutive syndrome may be a marker for relative perseveration for cholinergic neurons.

The validity of characterizing patients with dementia in terms of MRI-LA is also supported by findings showing that patients presenting with at least moderate MRI-LA accomplish fewer steps and make more errors on the Naturalistic Action Test, a test of instrumental activities of daily living/everyday action.[56] In this research, Naturalistic Action Test errors were also correlated with worse performance on tests of executive control.[56] Also, Disimone et al[57] found that treating patients with dementia with donepezil reduced executive errors on the Naturalistic Action Test. These relationships between MRI-LA and differential performance on neuropsychological tests, everyday action performance, and response to anticholinergic medication have important treatment implications. Chui et al[53] noted that in their autopsy series, vascular disease was quite heterogeneous. This is consistent with past studies suggesting that a wide variety of pathological processes may link vascular disease with AD, including mild ischemia sometimes termed "incomplete infarction,"[58] amyloid angiopathy of the penetrating pial vessels,[59,60] and lipohyalinosis of deep perforators.[61] A breach of the blood–brain barrier induced by atherosclerotic disease and beta-amyloid (Aβ) deposition within the walls of blood vessels[62,63] has also been associated with LA. Roher et al[64] have shown that for a subset of patients with AD, significant atherosclerosis and vascular stenosis of the large vessels in the circle of Willis is correlated with increasing hemispheric white matter disease. LA associated with AD has been linked to amyloid-induced oligodendrocyte toxicity.[65] Gurol et al[66] found an association between high levels of plasma Aβ-40 and increased white matter alterations in patients with AD. Linking these pathological mechanisms with patients who present clinically with MRI-LA and the neuropsychological syndromes described previously may shed needed light on the neurobiology of how vascular disease and AD interact.

The current research is not without limitations. First, only a few executive and language-related tests were used and the neuropsychological protocol used in the current research is different compared with Reed et al.[54] It is possible that a different outcome would have occurred if a wider array of tests was used. Second, as acknowledged previously, visual rating scales provide only a gross measure of white matter severity. A better research strategy might be to associate MRI pixel-based measures of both whole brain and regional white matter alterations with neuropsychological test performance. Finally, the current research did not include measures of the hippocampus and other important gray matter structures. Also, individuals without cognitive impairment were not included in the sample. Therefore, the generalizability of the current findings may be restricted to only those individuals with cognitive deficits.

In summary, despite these limitations, the data reported above provide an algorithm to operationally define how and when MRI-LA is making a meaningful contribution to the clinical expression of dementia.

Disclosures

None.

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