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Subcortical hyperintensities impact cognitive function among a select subset of healthy elderly

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Abstract

Previous studies have examined the impact of subcortical hyperintensities (SH), a proxy measure of cerebrovascular disease, on the cognitive abilities of otherwise healthy older adults. However, there remains a limited understanding as to what extent this MRI marker of pathological processes explains the decline in specific cognitive functions that occur nearly ubiquitously with advanced age, especially in relation to other age-related imaging markers. In the present study we compared cognitive abilities between a sample of 53 older healthy adults (age range = 50–79) and a sample of 53 younger adults (age range = 21–40). As expected, the older group performed significantly worse on most cognitive measures compared to the younger group. Frontal volume and total grey matter volume were also significantly reduced among the older individuals compared to the younger individuals. SH volume was consistently associated with cognitive function in older adults, though, this relationship was evident only for a relatively small subset of older individuals with the most severe SH. These data suggest that the relationship between SH and cognition in the elderly is driven by a subset of individuals who may be in the earliest stages of vascular cognitive impairment. Further, the findings suggest that cognitive aging is largely determined by factors other than SH for most older adults.

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1. Introduction

Cerebrovascular disease is remarkably common among the elderly and potentially contributes to cognitive function in this population. Cerebrovascular disease is evident on neuroimaging in the vast majority of individuals over the age of 65 (Almkvist, Wahlund, Andersson-Lundman, Basun, & Backman, 1992; Soderlund, Nyberg, Adolfsson, Nilsson, & Launer, 2003) with subcortical ischemic disease being particularly prevalent. Subcortical ischemic disease can be readily visualized on MRI as subcortical hyperintensities (SH) and to a lesser extent on computerized axial tomography. A number of studies have demonstrated that performance on measures of executive function and psychomotor speed are typically associated with increased SH in the healthy elderly (Gunning-Dixon & Raz, 2000). This finding is consistent with what has been reported between SH and cognition among individuals with mild vascular cognitive impairment (DeCarli et al., 2001; Kramer, Reed, et al., 2002) and individuals with vascular dementia (Cohen et al., 2002; Paul et al., 2003), suggesting that the relationship between SH volume and cognitive function falls along a continuum of cerebrovascular disease-related cognitive changes.

Given the high prevalence of SH among older individuals, it can be tempting to conclude that cognitive decline among in this population can be explained at least in part on their level of SH. However, there is reason to doubt this assumption, if factors associated with SH (e.g., hypertension) are adequately controlled. In this circumstance, SH may not be as common, and thus may not explain any significant degree of age-related cognitive decline for a subset of individuals. In one widely referenced study (Boone, Miller, et al., 1992), nearly half of a large sample of healthy adults exhibited no SH on MRI, however, individuals that exhibited significant SH (greater than a 10 cm² area of involvement) performed significantly more poorly than elderly individuals without evidence of SH. This study has been frequently referenced as evidence for a “threshold effect”, whereby a specific degree of SH is necessary to produce cognitive effects. These findings suggest that in the absence of significant SH, cognitive changes among the elderly are determined by alternative factors (e.g., regional cortical volume changes, metabolic changes, etc.).

The purpose of the present study is to examine the relationship between cognitive status and SH severity, frontal volume, frontal white matter volume, and total grey matter volume in the healthy elderly. Specifically, we were interested in comparing cognitive performance of an older cohort to that of a younger group of control subjects and subsequently determine whether SH and/or other neuroimaging markers adequately explained the severity of changes in cognitive decline associated with aging. We predicted that the older group would perform significantly more poorly than the younger control group on the cognitive measures, and that total SH volume would be strongly related to performance in the older cohort. We also hypothesized that each of the other neuroimaging markers (frontal grey volume and total grey volume) would independently correlate with cognitive status among the elderly.

2. Methods

2.1. Subjects

All individuals in the present study were participants in a large multi-site, multi-national study of brain function (Brain Resource International Database; Gordon, 2003). As part of the parent study, individuals were screened for any medical (e.g., diabetes, hypertension, stroke, degenerative disease, thyroid disease) or psychiatric condition that could interfere with cognitive function. Participants were required to complete a comprehensive web-based questionnaire that consisted of questions pertaining to personal and family history of medical and psychological difficulties. Participants also completed the Depression, Anxiety and Stress Scale (DASS; Lovibond & Lovibond, 1995) and the Composite International Diagnostic Interview (CIDI; Robbins, James, et al., 1998). Participants for the present study were examined at one of two research sites in Australia.

Two groups of participants were identified. We first identified all individuals over the age 50 who completed the cognitive testing and the MRI. This resulted in a sample of 53 individuals. We subsequently selected a cohort of 53 younger individuals who also had undergone cognitive testing and MRI. The older group averaged 59.4 years of age (S.D. = 8.1, range = 50–79) and 12.7 years of education (S.D. = 3.0). The younger cohort averaged 25.3 years of age (S.D. = 6.4, range = 18–39) and 12.9 years of education (S.D. = 1.0). Both younger and older individuals were recruited from regional communities. Written informed consent was obtained for all individuals after receiving a thorough explanation of the study. The parent study was approved by local IRBs at each of the participating research sites. Participants were financially compensated for completing the cognitive assessment and the MRI.

2.2. Neuropsychological assessment

The neuropsychological battery consisted of 12 tests administered on a computer using a touch-screen interface and voice recording via wav files. All instructions were provided via headphones, and each test was preceded by a thorough explanation, visual examples of performance, and a practice trial. Rates of completion of the cognitive battery did not differ between the two groups ($P < .05$). The individual tests are described below. Initial studies indicate that the battery has good validity (Paul et al., *in press*), and reliability (Williams, Paul, Clark, Cooper, & Gordon, *in press*).

2.2.1. Neuropsychological Battery

The battery of IntegNeuro™ tests tapped the following domains of cognitive function: sensori-motor, verbal and language, memory, executive planning and attention. Scoring of responses was conducted using an automated software program for most tests, and by hand-scoring for wav files. Trained research assistants conducted the hand scoring and oversight was implemented to monitor accuracy. For a complete description of the individual tasks see Gordon (2003). Briefly, the battery included the following measures: Simple Motor Tapping, Choice Reaction Time task, Digit Span, Switching of Attention Task (computer Version of Trail Making A and B), Verbal Interference (adaptation of the Stroop test; Golden, 1978):

Maze Task (adaptation of the Austin Maze; Walsh, 1985), Letter Fluency (FAS), and Animal Fluency.

2.3. Brain MRI acquisition

MRIs were obtained at two imaging centers. A 1.5T Siemens (Erlangen, Germany) Vision Plus system was employed at Westmead Hospital in Sydney Australia, and a 1.5T Siemens (Erlangen, Germany) Sonata was employed at Perrett Imaging, Flinders University, Australia. The imaging sequence was identical at both locations and included a 3D T1-weighted image acquired in the sagittal plane using a 3D MPRAGE sequence (TR = 9.7 ms; TE = 4 ms, Echo train: 7; Flip Angle 12 degrees; T1 = 200 ms NEX = 1). A total of 180 contiguous 1 mm slices were acquired with a 256×256 matrix with an in plane resolution of $1 \text{ mm} \times 1 \text{ mm}$ resulting in isotropic voxels. For SH quantification, dual echo sequences were obtained in axial view, with TR = 7529 ms, TE = 15/105, echo train = 7, Flip Angle = 180, FOV = $220 \text{ mm} \times 220 \text{ mm}$, NEX = 1, and pixel size = $.87 \times .86$. Slices were 3 mm thick and there was no gap. Preliminary analyses reveal no significant site differences in total grey matter (Grieve, Clark, Williams, Peduto, & Gordon, *in press*).

2.4. SH quantification

Subcortical and periventricular SH was quantified using the T2 images. The quantification procedure has been employed previously by our group to examine cerebrovascular disease in geriatric patients and individuals with vascular dementia (Jenkins, Malloy, et al., 1988). SH was quantified by calculating hyperintensities in the subcortical and periventricular areas, including thalamus, basal ganglia, and white matter tracts. The extent of SH was quantified using semi-automated thresholding methods to select pixel values representing abnormal brain tissue and ventricular space. WBV was calculated by determining total brain size minus the ventricles. The final dependent variable was SH ratio, determined by dividing SH total by WBV.

2.5. Cortical grey matter quantification

Voxel-based morphometry (VBM) was employed to define cortical grey matter volumes. MRI processing was performed using Statistical Parametric Mapping (SPM2) and MATLAB (MathWorks, Natick, USA). The VBM methodology used to process these data has been fully described in a previous publication (Grieve et al., *in press*). Briefly, all brains were spatially normalized to stereotactic space based on the ICBM 152 template (Montreal Neurological Institute). The anatomical designations were made in reference to the MNI coordinate system (Tzourio-Mazoyer et al., 2002). See Figure 1, for example of segmentations. We focused on frontal lobe volume, frontal white matter volume and total grey matter volume. Regions included in the total frontal volume included the entire cortical surface of the frontal lobes bilaterally. Frontal grey matter was selected as a primary dependent variable as this region appears vulnerable to age-related changes in volume (Gunning-Dixon & Raz, 2003).

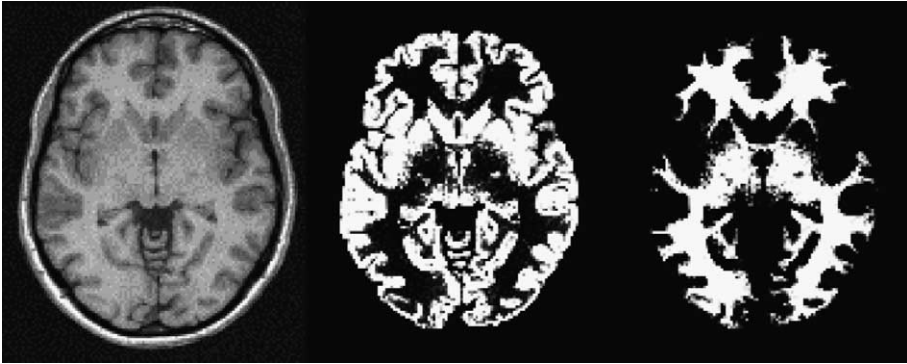


Fig. 1. A representative axial MRI image (panel 1) together with the corresponding grey matter segment (panel 2) and white matter segments (panel 3).

3. Results

3.1. Demographics

Education, depression scores, and neuroimaging indices are presented in Table 1. As noted above the older individuals reported a significantly lower number of depressive symptoms on the DASS than younger individuals ($P < .05$). SH was not quantifiable among the younger cohort, and therefore group differences were not computed. In contrast, the two groups differed significantly on frontal lobe volume ($P < .01$) and total grey matter volume ($P < .01$). In each analysis, the older adults had lower volumes than younger adults.

3.2. Cognitive performance and age

Comparisons of older and younger adults revealed significant differences on the most cognitive measures (Wilks' lambda = .44, $F(9, 64) = 8.9$, $P < .01$). Univariate contrasts revealed that younger individuals performed significantly better than the older individuals on all cognitive measures with the exception of the FAS task.

Table 1
Group differences on the neuroimaging variables: mean (S.D.)

Measure	Younger	Older	<i>F</i>
Education	12.9 (1.0)	12.7 (3.0)	0.2
DASS Depression	2.6 (3.6)	1.2 (1.8)	6.5*
SH ratio (voxels)	NA	0.7654 (2.02)	NA
Frontal grey matter	0.09271 (0.0029)	0.08917 (0.0033)	28.4**
Total grey matter	765, 528.4 (78, 299.6)	694, 230.8 (58, 182.1)	28.3**

* $P < .05$.

** $P < .01$.

Table 2
Correlations between cognitive measures and MRI indices among the older individuals

Measure	SH	Frontal grey	Total grey
Tapping—total correct	−.12	.00	.09
Choice RT	−.07	.03	−.25
Reverse Digits	−.04	.08	.08
Verbal Interference Score 2—color–word	−.33	.17	.36
Maze trials	.05	−.02	−.10
Maze errors	.38*	−.19	−.25
FAS (average/trial)	−.28*	.35*	.28*
Animals	−.30*	.24	.17
Switching of Attention—numbers	.42*	−.26	.10
Switching of Attention—numbers and letters	.10	−.17	−.17

* $P < .05$.

3.3. Relationship between SH and cognitive function

Correlations revealed that SH ratio was related to performance on several measures (see Table 2) for the older individuals. A higher ratio of SH to WBV was associated with poorer performance on Verbal Interference 2, Switching of Attention 1, Animal Fluency, FAS Fluency, and Maze errors. There were no significant relationships between SH ratio and performance on the other cognitive measures. Similarly, there was no relationship between SH ratio and depression.

3.4. Mild–moderate SH and cognitive function in the elderly

In order to examine the relationship between SH and cognitive function among individuals with less severe SH we examined the frequency of SH severity in the older sample. See Figure 1 for an example of more severe SH in the older group. From the histogram, it was apparent that more than 85% of the individuals in the sample had a SH/WBV ratio less than 1.00. By contrast, seven individuals (13%) had SH/WBV ratios that ranged from 1.25 to 11.04. Removing these seven individuals from the correlation analyses resulted in the loss of significant relationships between SH/WBV and cognition on each test ($r_s < .27$), despite retaining 46 individuals for the analyses. A between-group MANCOVA revealed that younger individuals performed better than older individuals with mild SH on all measures with the exception of FAS and Tapping (Wilks' lambda = .54, $F = 6.5$, $P = .05$).

In light of the results above, we then examined the correlations between SH/WBV and cognition for the group of seven individuals with the largest amounts of SH. Results of these analyses revealed robust correlations that mirrored those for the larger group. Specifically, SH/WBV was significantly related to lower score on Verbal Interference 2 ($r = -.95$), increased number of errors on the Maze Task ($r = .80$), lower score on FAS ($r = -.76$), lower score on the Animal Fluency ($-.59$), and longer time to complete Switching of Attention 1 (.80).

3.5. Correlations between grey matter volumes and cognitive function

Significant correlations were evident for only a few cortical and subcortical neuroimaging measures. Specifically, greater total grey matter volume was significantly associated with more correct responses on FAS verbal fluency ($r = .27, P < .05$) and on the color–word trial of the interference test ($r = .36, P < .05$). Total score on the FAS task was also significantly correlated with total frontal lobe volume ($r = .35, p < .05$). No other correlations were significant for total grey matter ($r_s < .26$) or frontal grey matter ($r_s < .26$).

4. Discussion

In the present study we demonstrated that increased levels of SH were associated with poorer cognitive status among older individuals. This finding is in accord with previous work (Gunning-Dixon & Raz, 2000) and supports the conclusion that SH is not a silent neuroimaging finding in the *healthy* elderly (Cook, Leuchter, et al., 2002). A new finding in the present study, however, is that the relationship between SH and cognitive abilities in the elderly may be driven by a relatively unique and restricted subset of individuals, while cognitive decline for most individuals is likely determined by factors other than SH.

Results suggest that SH is not the primary factor associated with age-related cognitive decline, but one of multiple processes that may impact the natural course of human aging and cognitive functioning of older adults. There is little question that a host of internal and external factors interact to influence senescence and therefore no single factor will account for the majority of variance in cognitive decline among the elderly. Consideration of this complex integration of multiple physiologic functions reveals that cognitive decline could be produced by a variety of mechanisms. The cumulative sum of all such mechanisms over an individual's lifetime would necessarily vary tremendously from that of another individual, thus creating challenges for researchers attempting to clarify “normal” aging behaviors and distinguish them from those due to pathology. An important distinction may exist between those processes that are “normal,” or an inherent part of aging, and those that are quite common but potentially avoidable (Mesulam, 2000).

It is important to note that the sample size in the present study was generally small, and therefore the results need to be replicated in a larger cohort of individuals. In addition, while standard structural MRI is a powerful modality for morphological and anatomical imaging, more recent imaging developments may have better sensitivity to detect age-related changes in microstructural integrity of the white matter. For example, diffusion tensor imaging (DTI) has been shown to detect age-related changes in the white matter not evident with structural imaging. These changes are believed to reflect microstructural changes in myelin, loss of axonal fiber integrity, and changes in extracellular space (Pfefferbaum et al., 2000). Additional studies are needed that employ DTI and sensitive functional imaging methods to understand the evolution of brain changes in the elderly. Use of existing databases that include cognitive, imaging and genetic data would be extremely beneficial to begin studies that define the genetic mediators of imaging and cognitive relationships.

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