White Matter Lesions and Cognitive Performance: The Role of Cognitively Complex Leisure Activity

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Background. Among persons with white matter lesions (WMLs), there is a range of cognitive function. We examine whether participation in leisure activities modifies the effect of WML load on cognitive function.

Methods. Data are from 2300 men and women (aged 66–92 years) participating in the population-based Age Gene/Environment Susceptibility-Reykjavik Study. Subcortical WML load was calculated as a weighted sum, based on size of lesions in the four lobes. Periventricular WML load was calculated as the sum of lesion scores, based on size, for the frontal caps, occipitoparietal caps and bands. The upper quartile of lesion load in either area was compared to the lower three quartiles. Composite scores of memory (MEM), speed of processing (SP), and executive function (EF) were constructed from a battery of neuropsychological tests. Frequency of participation in nine cognitively stimulating leisure activities was assessed via questionnaire; the upper quartile was compared to the lower three quartiles. Multiple regression, controlling for demographic and health factors and brain infarcts, was used to test the main effects and interaction of WMLs and leisure activity on cognitive function.

Results. High leisure activity was associated with higher performance in all three cognitive abilities: MEM β = 0.20, 95% confidence interval [CI], 0.11–0.29; SP β = 0.37, 95% CI, 0.29–0.45; and EF β = 0.23, 95% CI, 0.15–0.29. High WML load was associated with significantly lower performance in SP (β = −0.06, 95% CI, −0.13 to −0.01). The effect of WMLs on SP performance was modified by high leisure activity (p for interaction < .05).

Conclusion. Participation in cognitively stimulating leisure activity may attenuate the effect of WML pathology on cognitive performance.

Key Words: Epidemiology—Cognition—White matter lesions—Leisure activity.

WHITE matter lesions (WMLs) are likely to be ischemic in origin and are associated with several cardiovascular risk factors (1). WMLs also disrupt subcortical-frontal functions and are associated with an increased risk for cognitive impairment (2). However, there is a range of cognitive function from poor to good in persons with a high WML load, suggesting that some individuals may be able to compensate for the structural damage caused by the brain pathology (3,4). Investigating factors associated with high cognitive performance despite WML load may provide another unique perspective in identifying such protective factors.

One factor that has been hypothesized to improve an individual’s ability to cognitively compensate for brain pathology is leisure time activity such as doing crossword puzzles, playing bridge, and participating in clubs. Animal studies suggest that environmental complexity and richness can prevent cognitive decline and promote neurogenesis (5,6). Social and cognitive activity may reduce the stress response and associated hormones, enhancing synaptic activity and promoting more efficient brain recovery and repair (7,8).

Here, we examine whether the association of WMLs and cognitive function is modified by participation in cognitively complex leisure activities in a population-based sample of older adults. We hypothesize that the association between WML load and cognitive performance would be weaker in persons who participate in leisure activity compared to those who do not.

METHODS

The Age Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik is aimed at investigating the contributions of environmental factors, genetic susceptibility, and gene–environment interactions to the aging of the neurocognitive, cardiovascular, musculoskeletal, body composition, and metabolic systems. Details on the study design and the baseline AGES-Reykjavik assessments have been described elsewhere (9–12). Briefly, participants are from the cohort of men and women born in 1907–1935 and living in Reykjavik who were followed as a part of the Reykjavik Study (RS) initiated in 1967 by the Icelandic Heart Association (13). Since its inception, cohort members have participated in up to six examinations, and have been under...
continuous surveillance for vital events. In 2002 cohort members were re-invited to participate in AGES-Reykjavik. Here we report on the first 2300 participants who completed the AGES-Reykjavik examination that included a structured survey instrument, cognitive testing, and brain magnetic resonance imaging (MRI). The characteristics of these 2300 compared to all RS participants can be found in Harris and colleagues (9).

AGES-Reykjavik was approved by the Icelandic National Bioethics Committee (VSN 00-063) and by the Institutional Review Board of the U.S. National Institute on Aging, National Institutes of Health. Informed consent was signed by all participants.

**MRI Scanning and Reading Protocol**

**MRI acquisition.**—High-resolution MR images were acquired on a 1.5 T Signa Twinspeed system (General Electric Medical Systems, Waukesha, WI). The image protocol consisted of the following pulse sequences: a proton density (PD)/T2-weighted fast spin echo (FSE) sequence (time to echo (TE)1, 22 ms; TE2, 90 ms; repetition time (TR), 3220 ms; echo train length, 8; flip angle (FA), 90°; field of view (FOV), 220 mm; matrix 256 × 256), a fluid-attenuated inversion recovery (FLAIR) sequence (TE, 100 ms; TR, 8000 ms; inversion time, 2000 ms; FA, 90°; FOV, 220 mm; matrix 256 × 256), a T2*-weighted gradient echo type echo planar (GRE-EPI) sequence (TE, 50 ms; TR, 3050 ms; FA, 90°; FOV, 220 mm; matrix 256 × 256). The acquisition of these sequences was performed with 3 mm thick interleaved slices. Additionally, images were acquired with a T1-weighted three dimensional spoiled gradient echo (3D-SPGR) sequence (TE, 8 ms; TR, 21 ms; FA, 30; FOV, 240 mm; matrix 256 × 256, slice thickness, 1.5 mm). On a 70% random subsample, we also acquired diffusion-weighted images (DWI; Axial DWI b = 0 and b = 1000) (12). All images were acquired to give full brain coverage, and slices were angled parallel to the anterior commissure–posterior commissure line to give reproducible image views in the oblique-axial plane.

**WML rating scale.**—WMLs are considered present in the case of visible hyperintense signal on both T2-weighted and FLAIR images. The load of WMLs in the subcortical and periventricular regions is separately rated according to a scale with known properties (13). Subcortical WML (SCWML) are those that are supratentorial and that are not in the basal ganglia, internal capsule, and cortical ribbon and are not confluent with the periventricular region. SCWMLs are scored separately for the right and left hemispheres and the frontal, parietal, occipital, and temporal lobes. The rating scale provides a semiquantitative “volumetric” estimation for WMLs (mm³). The size of the lesion is measured at the largest diameter and categorized into small (≤ 3 mm), medium (4–10 mm), or large (>10 mm) lesions. Each size is given a weight to approximate volume, that number is multiplied by the number of lesions of the respective size, and they are all added together (14). Periventricular WMLs (PVWMLs) are those adjacent to the ventricular lining and are graded in the frontal caps, occipitoparietal caps, and bands. The grading scale is based on the size of the lesions: 0 (absent), 1 (>0–5 mm), 2 (6–9 mm), or 3 (≥10 mm). The total load of PVWMLs in the whole brain is calculated as the sum of lesion scores for the three areas over both hemispheres.

The sample was grouped into quartiles of SCWMLs and PVWMLs separately. Persons in the upper quartile of WML load for either SCWML or PVWML were compared to those in the lower three quartiles. Those in the lower three quartiles of WML load were the reference group. We included both SCWMLs and PVWMLs in the definition of high WML load because it is often difficult to distinguish the lesion areas, particularly in the case of confluent lesions, and it has been suggested that the two lesion types may not be distinct (15). In addition, there is considerable overlap in the upper quartile of PV and SC WMLs.

**Cerebral infarcts.**—Cortical infarct-like lesions were defined as parenchymal defects involving or limited to the cortical ribbon and surrounded by an area of high signal intensity on FLAIR images. Subcortical infarct-like lesions were defined as parenchymal defects not extending into the cortex that are surrounded by an area of high signal intensity on FLAIR images and that do not show evidence of hemosiderin in its walls on the EPI scan. Defects in the subcortical area with evidence of hemosiderin in its walls on EPI scans were considered remote hemorrhages or old hemorrhagic infarcts. Defects in the subcortical area without a rim or area of high signal intensity on FLAIR, and without evidence of hemosiderin were labeled as large Virchow-Robin spaces (VRS) (16); these VRS were not counted as subcortical infarcts.

**Brain volume.**—Estimated brain volume was available for the 70% of the sample that underwent DWI imaging. To assess intracranial volume (ICV), the outer contour of the subarachnoid space was manually delineated on each slice of the b0 images of the DWI sequence. This was followed by an automated segmentation procedure that assigned parenchymal volume (PV) and cerebrospinal fluid (CSF) within this region. Brain atrophy was estimated by the formula [(ICV − PV) / ICV]; this measurement reflects the amount of ICV that is CSP.

**Quality control procedures.**—Every 6 months the intra-observer variability for each observer and every 3 months the inter-observer variability for the whole group of observers were assessed. The intra-observer weighted κ statistics were 0.89 for global WMLs and 0.92 for parenchymal defects; the inter-observer variability for the whole group of observers was assessed. The intra-observer weighted κ statistics were 0.71 for global WMLs and 0.66 for parenchymal defects.

**Measures of Cognitive Function**

The cognitive test battery included multiple tests of three cognitive domains. Similar to other population-based studies (2,17) we constructed composites scores of memory (MEM), speed of processing (SP), and executive function (EF) based on a theoretical grouping of tests. The MEM composite includes a modified version of the California
Verbal Learning Test (18) immediate and delayed recall. The SP composite includes Digit Symbol Substitution Test (DSST; 19), Figure Comparison (20), and a modified Stroop Test (21) Parts I (Word Reading) and II (Color Naming). The EF composite includes Digits Backward (19), the CANTAB Spatial Working Memory Test (22), and the Stroop Test Part III (Word-Color Interference). A confirmatory factor analysis (CFA) was used to check the fit of the composites to the data; results indicated that the three-factor structure fit the data reasonably well ($\chi^2_{24} = 434; \text{normed fit index } [NFI] = 0.94; \text{incremental fit index } [IFI] = 0.94; \text{comparative fit index } [CFI] = 0.94; \text{root mean square error of approximation } [RMSEA] = 0.09$) (23).

All tests were normally distributed in the cohort, and inter-rater reliability was excellent (Spearman correlations range from 0.96 to 0.99 for all the tests). Composite measures were computed by converting raw scores on each test to standardized $z$ scores and averaging the $z$ scores across the tests in each composite.

**Diagnosis of Dementia**

Dementia case ascertainment was a three-step process. The Mini-Mental State Examination (MMSE; 24) and the DSST (19) were administered to all participants. A second, diagnostic test battery was administered to individuals who screened positive based on a combination of these tests (<24 on the MMSE or <18 on the DSST. Based on their performance on the Trails B (25) and the Rey Auditory Verbal Learning test (26), a subset of these individuals went on to a third step. This step included a neurologic examination and a proxy interview about medical history and social, cognitive, and daily functioning relevant to the diagnosis. A consensus diagnosis of dementia based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) guidelines (27) was made by a panel that included a geriatrician, neurologist, neuropsychologist, and neuroradiologist.

**Leisure Activity**

Participants answered questions about time spent on 10 leisure activities: doing crossword puzzles; reading; attending religious services or meetings; playing board or card games; using the computer; writing letters or poems; doing artwork, carpentry, or sewing; attending a performance or movie; attending a class, lecture, or public meeting; and participating in community, church, or social clubs. Participants reported the frequency of participation in each activity during the past 12 months as “daily,” “at least once weekly,” “at least once monthly,” “every few months,” or “never.” Because 95% reported daily reading, this activity was dropped from the leisure activity score. To make the activity more relevant to daily activity, we recoded the response categories (i.e., 30 points for daily participation, 14 points for at least once per week participation, 1.5 points for at least once per month participation, 0.5 points for less than once a month participation, and 0 points when reporting never participating in an activity).

A summary score (days per month active) was created representing overall leisure activity (9 activities). Points were averaged across the activities; the score ranged from 0 to 30 representing the “average” number of days per month of participation in leisure activity. We categorized the sample by quartiles of leisure activity; the highest quartile was compared to the lower three quartiles, which served as the reference group.

**Additional Covariates**

Based on previous reports we adjusted for demographic (age, sex, education) and health variables. Depression may be related to WML and may influence cognitive performance (28). High depressive symptomology was classified as a score of ≥6 on the 15-item Geriatric Depression Scale (29). Because vascular factors are associated with WML (1) and may influence cognitive performance (30,31), we also adjusted for several vascular risk factors: hypertension (self-reported hypertension, use of hypertensive medications, or measured systolic blood pressure of ≥140 or diastolic blood pressure ≥90), diabetes (self-report of a physician’s diagnosis of diabetes, use of diabetes-related medications, or fasting blood glucose ≥7.0 mmol/L (32)), smoking status (ever vs never smoker) and apolipoprotein E allele (any ε4 vs no ε4). Calcium in the coronary arteries was quantified using computerized tomography images and a calcium scoring software. Results were expressed in Agatston scores (33) and log transformed for the regression analyses. Current moderate/vigorous physical activity was assessed via questionnaire and categorized as never (reference), rarely, <1 hour/week, 1–3 hours/week, 4–7 hours/week, or >7 hours/week. Finally, because brain infarcts may be associated with impaired cognitive function (34), we adjusted for cortical and subcortical infarcts. In a subanalysis on 70% of the sample, we also adjusted for brain volume.

**Analytical Sample and Strategy**

Of the 2300 participants, 158 were excluded based on standard MRI contraindications (35), and an additional 122 did not get full MRI scans due to claustrophobia, equipment failure, refusal, or choosing only to participate in an in-home examination, giving a sample of 2020 MRI scans. Of the 2020 participants with MRI scans, 1787 had complete neuropsychological data. Compared to the 1787 with complete data, the 513 with any missing data were significantly older (78.1 vs 75.7 years, $p < .001$), had a higher prevalence of diabetes (16% vs 11%, age-adjusted $p = .003$), had lower median MMSE scores (25.0 vs 28.0, age-adjusted $p < .001$), and had lower mean DSST scores (26.0 vs 30.0, age-adjusted $p < .001$). Education level, sex, and prevalence of hypertension and depression did not differ between the two groups.

**Statistical Analysis**

Baseline characteristics of participants in the upper quartile were compared to those in the lower three quartiles for WML load and leisure activity and in the four groups of WML and leisure activity level: Low (lower three quartiles) WML/Low activity; Low WML/High activity; High (upper quartile) WML/Low activity; High WML/High activity. Age-adjusted analysis of variance was used to compare
continuous variables, and the chi-square statistic was used for categorical variables. For each cognitive ability, two multivariate linear regression models were tested. The first model examined the main effects of WML load and leisure activity and was fully adjusted for the confounders listed above. The second model included the same confounders plus an interaction term of WML \times \text{Leisure activity} to determine whether the association of WML load and cognitive performance differed in participants with high and low leisure activity. The Low WML/High leisure activity group was the reference group because we expected this group to perform best. We expected the High WML load/Low leisure activity group to perform worst. We expected the High WML load/Low leisure activity group also to have less physical activity and low leisure activity. The Low WML/High leisure activity group had higher average performance in MEM and EF. The High WML load/Low leisure activity group had higher performance on all three cognitive abilities (Table 2, Model 1).

**RESULTS**

Compared to participants in the lower three quartiles of WML load (n = 1195), those in the upper quartile (n = 592) were significantly older (77.1 vs 75.1, p < .001) and had a higher prevalence of hypertension (84% vs 75%, age-adjusted p < .01), diabetes (14% vs 9%, age-adjusted p < .001), depression (8% vs 5%, age-adjusted p = .02), and cerebral infarcts (42% vs 26%, age-adjusted p < .001). Participants in the upper quartile of WML load were also more likely than those in the lower three quartiles to have high coronary calcium load (29% vs 21%, age-adjusted p < .01) and low education (28% vs 20%, age-adjusted p < .01), and to be physically inactive (51% vs 41%, age-adjusted p < .05).

Compared to the Low WML/High activity group, the three other groups (Low WML/Low activity, High WML/ Low activity, High WML/High activity) were older, had lower levels of education, were more likely to be physically inactive, and had lower EF performance (Table 1). The Low WML/Low activity group also had fewer women and lower SP and MEM performance compared to the Low WML/ High activity group. Compared to the Low WML/High activity group, the High WML/Low activity group had a higher prevalence of depression and diabetes and lower SP and MEM performance. The High WML/High activity and High WML/Low activity groups were more likely to have cerebral infarcts and high coronary calcium load compared to the Low WML/High activity group.

In fully adjusted main effects models, participants in the upper quartile of WML load had significantly slower SP (Table 2, Model 1). Compared to participants in the lower three quartiles of WML load, those in the upper quartile of WML load also had poorer test scores on MEM and EF, although these comparisons did not reach statistical significance. Participants in the upper quartile of leisure activity had higher performance on all three cognitive abilities (Table 2, Model 1).

Leisure activity level modified the association of WML to performance on SP (Table 2), such that participants in the upper quartile of WML load who were also in the upper quartile of leisure activity (High WML Load/High activity) performed better than those in the upper quartile of WML load who were in the lower three quartiles of leisure activity group (High WML Load/Low activity), as well as those in the lower three quartiles of WML load, irrespective of the level of leisure activity (see Table 3 total sample model for adjusted mean scores; Figure 1A and B). The interaction was significant for SP [p for interaction < .05] and, although not statistically significant for MEM [p for interaction = .22], the pattern of results is similar (Figure 1A and B). The association of WML load with EF performance did not vary by level of leisure activity (Figure 1C). In the subgroup that had a measure of brain atrophy (Table 3, brain atrophy model), the High WML/High activity group had higher average performance in MEM and
SP than the High WML/Low activity group. In this smaller sample, the interaction term for WML load and leisure activity for SP was $p = .07$. We also repeated the analysis excluding participants who were demented. The results did not change. For MEM and SP, participants with High WML/High activity performed better on average than all other groups (Table 3, nondemented only model). The interaction term did not reach significance (SP $p = .14$).

**Discussion**

As expected, we found that participants in the upper quartile of WML load performed worse on cognitive tests, particularly those that measure speed of processing. Participants in the upper quartile of WML load were sicker in general, with higher prevalence of various cardiovascular risk factors. However, there was variability in cognitive function in the group with high WML load; we hypothesized that leisure activity may contribute to this variability. We found that participation in cognitively stimulating leisure activity attenuated the effect of WML pathology on SP performance. Based on the secondary analysis controlling for brain volume, and the secondary analysis excluding demented participants, the pattern of results was not different and the effect modification of leisure activities on SP remained important. Thus, our findings suggest that, despite high WML pathology, there may be behavioral factors that can buffer the adverse effects of WML.

This study has a number of strengths. First, the use of composite scores allowed us to examine specific cognitive abilities that are more susceptible to WML pathology. Second, we have assessed participation in a wide range of leisure activities that represent both individual and group activities. Third, health status is well characterized in our sample, so we could adjust for a number of potential confounders.

However, the results should be interpreted with limitations of the study in mind. Because findings are cross-sectional, we do not know whether leisure activity patterns are a cause or an effect of variability in cognitive function. This will be examined in a planned follow-up. Furthermore, we only examined whether the total amount of leisure activity attenuated the effect of WML pathology on cognitive performance. It is possible that individual activities are more or less effective modifiers of the WML–cognition association.

High WML load reflects high levels of small vessel disease, which may result in reduced conduction of action

**Table 2. Linear Regression $\beta$ Values and 95% Confidence Intervals (95% CI) of White Matter Lesions (WMLs) and Leisure Activity and Cognitive Function for Total Sample ($N = 1787$)**

<table>
<thead>
<tr>
<th>Main Effects</th>
<th>Memory $\beta$ (95% CI)</th>
<th>Speed of Processing $\beta$ (95% CI)</th>
<th>Executive Function $\beta$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Model 2</td>
<td>Model 1</td>
</tr>
<tr>
<td>WML load (high vs low)</td>
<td>$-0.06 (-0.15, 0.02)$</td>
<td>$-0.09 (0.18, 0.01)$</td>
<td>$-0.06* (-0.13, -0.01)$</td>
</tr>
<tr>
<td>Leisure activity (high vs low)</td>
<td>$0.20^2 (0.11, 0.29)$</td>
<td>$0.17^2 (0.07, 0.28)$</td>
<td>$0.37^1 (0.29, 0.45)$</td>
</tr>
<tr>
<td>Interaction of WML $\times$ Leisure activity</td>
<td>$-$</td>
<td>$0.11 (-0.07, 0.30)$</td>
<td>$-$</td>
</tr>
</tbody>
</table>

**Notes:** Model 1 = main effects model Adjusted for age, education, sex, depression, body mass index (BMI), myocardial infarction (MI), total cholesterol, apolipoprotein E (ApoE) genotype, hypertension, and smoking status. Model 2 = high WML $\times$ High Leisure activity interaction term included. Adjusted for age, education, gender, depression, BMI, MI, total cholesterol, ApoE genotype, hypertension, smoking status, and cerebral infarcts.

Note: $p < .05$; $p < .01$; $^1 p < .001$. 

**Table 3. Adjusted Means of Cognitive Performance for Groups of White Matter Lesion (WML) Load and Leisure Activity**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Low WML Load</th>
<th>High WML Load</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High Leisure Activity ($N = 339$)</td>
<td>Low Leisure Activity ($N = 856$)</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample ($n = 1787$)</td>
<td>0.19</td>
<td>0.02</td>
</tr>
<tr>
<td>Adjusted for brain atrophy ($n = 1174$)</td>
<td>0.22</td>
<td>0.02</td>
</tr>
<tr>
<td>Nondemented only ($n = 1720$)</td>
<td>0.21</td>
<td>0.06</td>
</tr>
<tr>
<td>Speed of processing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>0.28</td>
<td>-0.04</td>
</tr>
<tr>
<td>Adjusted for brain atrophy</td>
<td>0.31</td>
<td>-0.02</td>
</tr>
<tr>
<td>Nondemented only</td>
<td>0.31</td>
<td>0.01</td>
</tr>
<tr>
<td>Executive function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample</td>
<td>0.20</td>
<td>-0.03</td>
</tr>
<tr>
<td>Adjusted for brain atrophy</td>
<td>0.25</td>
<td>-0.01</td>
</tr>
<tr>
<td>Nondemented only</td>
<td>0.21</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Note:** Group $n$ values are for total sample ($N = 1787$). All models were adjusted for age, education, gender, depression, body mass index, myocardial infarction, total cholesterol, apolipoprotein E genotype, hypertension, smoking status, and cerebral infarcts.
potentials over long fiber tracts in the brain (36). However, neuronal degeneration and other brain pathologies may have a different effect on cognitive function, and may in part explain our findings. More detailed information on atrophy in selected regions of interest, such as the hippocampus or frontal and prefrontal cortex, is needed to further understand the role of atrophy in modifying cognitive performance (37,38).

There are a number of specific mechanisms by which participation in cognitively stimulating leisure activity may help maintain cognitive function in persons with high vascular risk profiles. Such activities could promote more efficient use of intact brain circuitry or a successful functional reorganization (4,39). Leisure activity may alter the stress response and associated hormones (40), or influence the architecture of the brain to increase the density of neurons (7), promote synaptogenesis and myelination (8), and enhance the cerebrovasculature (41). Clinical and animal studies suggest that environmental and behavioral factors may influence white matter through myelination (42,43). The relative strength of the association between leisure activity and SP ability in those with high WML could more specifically reflect an association between leisure activity (environment), SP, and speed of conduction in the brain that is mediated through myelination and integrity of white matter tracts (36).

The magnitude of difference in performance within the upper quartile of WML load by level of activity is approximately .25 standard deviation (SD) for MEM and EF and nearly .5 SD for SP. In our sample, there is approximately a .25 SD decrease in MEM and SP, and a .20 decrease in EF for every 5 years of increasing age. Although there are no clinically relevant benchmarks for performance in the composites scores on which we report, the difference in performance observed between the high and low activity groups in persons with high WML load corresponds to, on average, 5 years of age for MEM and EF and 5–10 years for SP.

These findings need replication in longitudinal studies. However, they already suggest that sociobehavioral factors may attenuate the effect of brain changes on cognitive performance, particularly in processing speed. With replication and further examination of whether specific activities mediate the relationship between WML pathology and cognitive performance, these findings may have implications for the design of intervention trials. As the prevalence of vascular diseases increases, cognitive impairment will become an important public health issue.
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