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Neuroticism and white matter hyperintensities

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ABSTRACT

Neuroticism is a major risk factor for neurodegenerative disorders, such as Alzheimer's disease and related dementias. This study investigates whether neuroticism is associated with white matter hyperintensities and whether this measure of brain integrity is a mediator between neuroticism and cognitive function. Middle-aged and older adults from the UK Biobank (N = 40,602; aged 45–82 years, M = 63.97, SD = 7.66) provided information on demographic and health covariates, completed measures of neuroticism and cognition, and underwent magnetic resonance imaging from which the volume of white matter hyperintensities was derived. Regression analyses that included age and sex as covariates found that participants who scored higher on neuroticism had more white matter hyperintensities ($\beta = 0.024$, 95% CI 0.015 to 0.032; $p < .001$), an association that was consistent across peri-ventricular and deep brain regions. The association was reduced by about 40% when accounting for vascular risk factors (smoking, obesity, diabetes, high blood pressure, heart attack, angina, and stroke). The association was not moderated by age, sex, college education, deprivation index, or APOE e4 genotype, and remained unchanged in sensitivity analyses that excluded individuals with dementia or those younger than 65. The mediation analysis revealed that white matter hyperintensities partly mediated the association between neuroticism and cognitive function. These findings identify white matter integrity as a potential neurobiological pathway that accounts for a small proportion of the association between neuroticism and cognitive health.

1. Introduction

White matter hyperintensities (WMH; also referred to as leukoaraiosis) are relatively common in magnetic resonance imaging (MRI) brain scans of older adults (Alber et al., 2019; Wardlaw et al., 2015). WMH are probably due to small vessel vascular lesions, dilated perivascular space, demyelination, gliosis, and axonal degeneration (Humphreys et al., 2021). The white matter structure deterioration that presents as WMH is strongly related to age and tends to be more common among people with vascular risk factors, including hypertension, obesity, and diabetes (Humphreys et al., 2021). The clinical relevance of white matter integrity has been shown in multiple prospective studies that link WMH to increased risk of stroke, dementia, and mortality (Debette and Markus, 2010). For example, a meta-analysis of 36 prospective studies (N = 19,040) found WMH were associated with a 14% increased risk of all-cause dementia, 25% increased risk of Alzheimer's disease, and 73% increased risk of vascular dementia (Hu et al., 2021). WMH have further been associated with cognitive function and decline (Jokinen et al., 2020; Kloppenborg et al., 2014) and measures of education and socioeconomic conditions (Waldstein et al., 2017). There is also a growing literature on the association of WMH with other functional parameters, including abnormal gait and balance (de Laat et al., 2011). However, less is known about how fundamental psychological dispositions are related to white matter integrity, particularly trait

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measures of psychological distress (Greenberg et al., 2021; Wang et al., 2014). Similar to metabolic dysfunction, psychological stressors can disrupt brain homeostasis and, over time, erode brain integrity.

Neuroticism is the most prominent personality trait that assesses relatively stable tendencies to experience more frequent and intense negative emotions (Cuijpers et al., 2010; Kern and Friedman, 2011). Individuals who score higher on neuroticism tend to be more vulnerable to stress and engage in maladaptive coping strategies (Gunthert et al., 1999). Neuroticism is a major predictor of psychiatric conditions, including anxiety and depression (APA, 2013; Kotov et al., 2010). Neuroticism is also robustly related to neurodegenerative diseases. Large studies and meta-analyses have shown that neuroticism is consistently associated with the risk of Parkinson's disease (Terracciano et al., 2021b) and Alzheimer's disease and related dementias (Aschwanden et al., 2021; Duchek et al., 2020), including vascular dementia (Terracciano et al., 2021a). Neuroticism is also associated with cognitive functioning and decline (Graham et al., 2021; Sutin et al., 2023), behavioral risk factors, such as smoking (Hakulinen et al., 2015) and physical inactivity (Sutin et al., 2016; Wilson and Dishman, 2015), slow gait (Stephan et al., 2018), and markers of metabolic dysfunction, from mitochondrial DNA to metabolic syndrome (Oppong et al., 2022; Phillips et al., 2010).

Based on the extensive literature that links neuroticism to health and cognition, this study tested the hypothesis that individuals who score high on neuroticism have more extensive WMH. To our knowledge, three cross-sectional studies have investigated this association, and most have reported null findings. A study from the UK (N = 565)(Booth et al., 2014) and one from South Korea (N = 397)(Byun et al., 2020) found no association. However, a study of 235 individuals from China (Yao et al., 2022) found that high scores on a neuroticism-related trait were associated with more WMH. The findings have also been mixed on the association between WMH and depression (Schuurmans et al., 2023), with a meta-analysis (N = 5876) reporting no association (odds ratio 1.12, 95% confidence interval 0.96–1.30, p = .14)(Wang et al., 2014). From this literature, it is clear that if there is any association between neuroticism and WMH, the association will likely have a small effect size and require a large sample to detect it reliably. Thus, this study tested the concurrent association between neuroticism and WMH in a large population-based sample. Because of potential regional differences (and related distinctions in pathophysiology and functional correlates), in addition to the total WMH, we tested whether neuroticism is differentially associated with deep and periventricular WMH. Moreover, we assessed whether a potential association between neuroticism and WMH is independent of socioeconomic conditions and vascular risk factors. We further conducted exploratory analyses to test whether demographic factors and the APOE genotype moderated the association. These moderation analyses evaluate whether the association generalizes across subgroups in the population (e.g., female vs. male). These analyses also explore whether high neuroticism has synergistic detrimental effects on WMH when combined with other risk factors for neurodegeneration, such as older age, lower education level, socioeconomic deprivation, or APOE e4 carrier status. Finally, we tested whether WMH and vascular factors mediate the association between neuroticism and cognitive function to further understand the pathways that link neuroticism to cognitive health.

2. Methods

Participants. The data were from the UK Biobank, which recruited over 500,000 individuals registered with the UK National Health Service (NHS) for a baseline assessment between 2006 and 2010. This study used data from the third wave (2014+) that included a neuroimaging substudy with assessment of WMH. In the main analysis, we included all individuals with data on neuroticism and WMH, without exclusions. The overall UK Biobank protocol is available online (http://www.ukbiobank.ac.uk). The study complies with the principles of the Declaration of Helsinki, the protocol was approved by the local institutional review board (North West Multicenter Research Ethics Committee), and all participants gave informed consent. The UK Biobank data are available to researchers who apply with UK Biobank. We obtained UK Biobank data through Application Reference Number 57672.

Personality assessment. Neuroticism was the only major personality trait assessed in the UK Biobank. A short form of the Eysenck Personality Questionnaire-Revised (EPQ-R)(Eysenck et al., 1985) was used to assess it. The EPQ-R scale had 12 items (e.g., "Are you a worrier?"), and the UK Biobank used the response options, Yes (1), No (0), Do not know, or Prefer not to answer. As in previous research (Terracciano et al., 2021b), the analyses included participants who responded Yes or No to at least nine items (11.7% had one missing response, 4.5% had two missing responses, and 2% had three missing responses). The mean across the 12 items was transformed into z-scores for the continuous analyses, with higher scores indicative of higher neuroticism.

White matter hyperintensities. This study used secondary data collected and processed by the UK Biobank. Full information on the acquisition protocols, the image processing pipeline developed and run on behalf of the UK Biobank, and the derived measures has been previously reported (Alfaro-Almagro et al., 2018); see also https://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1977. The imaging data were collected using Siemens Skyra 3T, with a standard Siemens 32-channel RF receive head coil. Total, deep, and periventricular white matter hyperintensity volumes were calculated based on T1 and T2 Fluid Attenuated Inversion Recovery (FLAIR) scans using the Brain Intensity Abnormality Classification Algorithm (BIANCA)(Griffanti et al., 2016). White matter hyperintensity volumes (mm^3) were log-transformed because of the positively skewed distribution (skewness = 4.21 and kurtosis = 28.87). The log transformed total volume of WMH had acceptable skewness = 0.13 and kurtosis = 0.07 (Supplementary Table S2 and Figs. S1–S3 illustrates WMH distribution before and after log-transformation).

Demographic Covariates/moderators. Age in years and sex (0 = male, 1 = female) were included in all analyses. Follow-up analyses included education (1 = college/university degree or equivalent, 0 = no) and the Townsend deprivation index, a proxy for socioeconomic status assigned to participants based on their postcodes. The Townsend deprivation index is based on unemployment, non-home ownership, non-car ownership, and household overcrowding in a geographic area. The presence/absence of the APOE e4 allele was determined from rs7412 and rs429358.

Vascular covariates/mediators. Vascular risk factors and conditions included reported doctor-diagnosed diabetes, high blood pressure, heart attack, angina, and stroke (1 = yes, 0 = no). It also included obesity (body mass index >30) and ever vs. never smokers (1 = ever, 0 = never). These variables were summed into a vascular index (ranged 0 to 7) for mediation analyses.

Cognition. A composite cognitive function was the average score from six tests administered at the assessment center during the third wave or the 2014 web-based administration. Supplementary Table S1 provide a description of the tests. The tests were (1) fluid intelligence, a measure of verbal and numerical reasoning; (2) prospective memory; (3) alphanumeric trail making, generally considered a measure of executive function; (4) symbol digit substitution, a measure of processing speed/reaction time; (5) maximum digits remembered, a measure of short-term numeric memory; and (6) pairs matching, a measure of visual short-term memory. The scores were transformed as needed (e.g., trail), coded with higher scores that indicated better performance, and z-scored before averaged. Because sample size varied by cognitive tests, the average was computed if at least three of the six test scores were available. All six scores were positively correlated and the internal consistency was Cronbach's alpha = 0.65. These brief UK Biobank cognitive measures have shown adequate reliability and validity (Fawns-Ritchie and Deary, 2020; Lyall et al., 2016).

Statistical analyses. Descriptive statistics for the study variables were computed as means and standard deviations (SD) or proportions. Linear regression was used to examine the association between neuroticism and WMH. Model 1 included age and sex, model 2 added college education and the Townsend deprivation index, and model 3 further included the vascular covariates. Multicollinearity was checked with Variance Inflation Factor (VIF), which was about 1 for all variables, suggesting that there was no multicollinearity. Age, sex, college education, deprivation index, and APOE genotype were tested as moderators in separate regression models by testing the neuroticism × moderator interaction. All variables were z-scored before the analyses, and all models included age and sex as covariates. Two sensitivity analyses examined the association after excluding individuals who received a diagnosis of dementia at any point in the study or those who were younger than 65 years. Model 4 from the PROCESS tool was used to test mediation (Hayes, 2017). The model controlled for the sociodemographic covariates; neuroticism was the independent variable, and cognition was the outcome. We first tested WMH as the sole mediator (path a: neuroticism predictor of WMH; path b: WMH predictor of cognition; path c and c': total and direct effect of neuroticism on cognition) and then we added the vascular index as a simultaneous mediator. We calculated the proportion of the total effect accounted for by the mediator (i.e., proportion mediated; ab/c or equivalently 1 - c'/c) and calculated confidence intervals using 5000 bootstrapped re-samples and 95% bias-corrected confidence intervals.

3. Results

All participants with data on neuroticism and WMH were included in the analyses (N = 40,602). Descriptive statistics for the study variables are in Table 1. The age of the sample ranged from 45 to 82 years, with an average of almost 64 years, and similar numbers of females and males, and similar proportions of those with and without college education.

Results of the regression models for total WMH are in Table 2. Across regression models that accounted for demographic, socioeconomic, and health-related covariates, higher neuroticism was consistently associated with higher WMH volume. The socioeconomic covariates included in model 2 had a small impact, but the vascular risk factors included in model 3 attenuated the association between neuroticism and WMH by roughly 40% [(β_{model1} - β_{model3})/β_{model1} x 100]. The effect size of neuroticism was very small but similar in magnitude to the socioeconomic variables, and significantly smaller than major risk factors for WMH, such as age, obesity, and hypertension. Neuroticism also had similar associations with WMH in deep (β = 0.021; 95% CI 0.011, 0.030; p < .001; n = 40587) and peri-ventricular (β = 0.023; 95% CI 0.015, 0.032; p < .001; n = 40587) brain regions, controlling for age and sex.

Separate regression models found that age, sex, college education, deprivation index, and APOE e4 variant did not moderate the association between neuroticism and WMH (all interaction terms, p > .05). The association between neuroticism and WMH was unchanged in a sensitivity analysis that excluded 76 cases diagnosed with dementia before or after the WMH assessment (β = 0.024; 95% CI 0.015, 0.032; p < .001). In another sensitivity analysis, results were essentially unchanged when participants younger than 65 were excluded (N = 20,173; β = 0.025; 95% CI 0.011, 0.037; p < .001).

The results of the mediation analysis are in Fig. 1. Both neuroticism (b = -.0667, SE=.0050, p < .001) and WMH (b = -.0636, SE=.0057, p < .001) were associated with cognitive function, controlling for age and sex. WMH volume was a significant mediator (indirect effect = -.0014, SE=.0003, p < .001) that accounted for about 2% (proportion of mediation) of the total effect between neuroticism and cognition. In a follow-up analysis, we added college education and the deprivation index as additional covariates and the vascular risk index as an additional mediator. The results indicated that neuroticism (b = −.0506, SE=.0049, p < .001) and WMH (b = -.0539, SE=.0056, p < .001) remained significant predictors of cognitive function, and WMH remained a significant mediator (indirect effect = -.0011, SE=.0003, p < .001; 2% proportion of mediation). Neuroticism was also associated with the vascular risk index (b=.0799, SE=.0051, p < .001), but the vascular risk index was not a significant predictor of cognition (b = -.0091, SE=.0050, p = .0651) and did not mediate the association between neuroticism and cognition.

Table 1
Descriptive statistics for all study variables.

Variable	N	Mean (SD) or % (n)
Age (years)	40602	63.97 (7.66)
Sex (male)	40602	47.1% (19137)
College education	40602	46.3% (18795)
Deprivation index	40564	−1.89 (2.72)
APOE e4 present	33924	23.1% (9372)
Current smokers	40602	3.4% (1366)
Former smokers	40602	33.7% (13702)
Obesity	39272	17.4% (7081)
Diabetes	40496	5.2% (2098)
Hypertension	40594	22.2% (9004)
Stroke	40594	0.9% (363)
Angina	40594	1.9% (766)
Heart attack	40594	1.3% (543)
Vascular burden	40594	0.86 (0.93)
White Matter Hyperintensity (mm^3)	40602	5125.87 (6781.66)
Log White Matter Hyperintensity	40602	8.02 (1.01)
Peri-ventricular White Matter Hyperintensity (mm^3)	40587	4032.34 (4742.61)
Log Peri-ventricular White Matter Hyperintensity (mm^3)	40587	7.82 (0.99)
Deep White Matter Hyperintensity (mm^3)	40587	1085.80 (2486.01)
Log Deep White Matter Hyperintensity (mm^3)	40587	6.01 (1.38)
Neuroticism	40602	0.29 (0.26)
Cognition	37959	0.02 (0.62)

Table 2
Results from regression models with neuroticism and covariates predicting white matter hyperintensity (WMH).

	Model 1	Model 2	Model 3
	B (95% CI)	B (95% CI)	B (95% CI)
Neuroticism	.024 (.015, .032)**	.022 (.013, .030)**	.014 (.005, .022)**
Age (years)	.510 (.502, .518)**	.510 (.501, .518)**	.497 (.488, .506)**
Sex (male)	.056 (.047, .064)**	.056 (.048, .065)**	.041 (.033, .050)**
College education		−.024 (−.033, −.016)**	−.011 (−.019, −.003)*
Deprivation index		.015 (.006, .023)**	.003 (−.005, .012)
Current smokers			.036 (.028, .045)**
Former smokers			.024 (.016, .033)**
Obesity			.078 (.070, .087)**
Diabetes			.036 (.027, .044)**
Hypertension			.080 (.072, .089)**
Stroke			.016 (.008, .025)**
Angina			.006 (−.003, .015)
Heart attack			−.005 (−.014, .003)

Note. Model 1 N = 40602, Model 2 N = 40564, Model 3 N = 39128. CI = Confidence interval.
*p < .05, **p < .01.

4. Discussion

Neuroticism is a relatively stable personality trait that has replicable and widespread associations with psychiatric and neurodegenerative diseases (Aschwanden et al., 2021; Terracciano et al., 2021b). This study

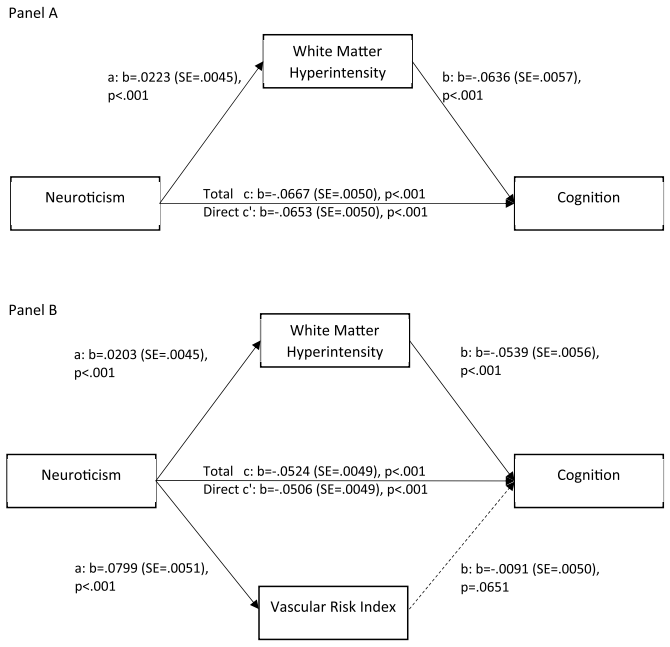

Fig. 1. Mediation models testing White Matter Hyperintensity and vascular index in the pathway between neuroticism and cognition.
Note. Panel A: N = 37959; Age and sex included as covariates. Panel B: N = 37916; Age, sex, college education, and deprivation index included as covariates. The two unstandardized coefficients c paths represent the b before (c) and after (c') the addition of mediator(s) into the model.

extends knowledge on personality and brain health by identifying an association between neuroticism and WMH, a marker of white matter integrity. The association between neuroticism and WMH was (1) found in a sample that was about 100-fold larger than samples examined in previous studies (Booth et al., 2014; Byun et al., 2020; Yao et al., 2022); (2) consistent across deep, peri-ventricular, and total volumes of WMH; (3) independent of demographic, socioeconomic, and vascular risk factors; (4) not moderated by age, sex, college education, deprivation index, or APOE e4 genotype. The study further found evidence that WMH mediate the association between neuroticism and cognitive function, supporting the hypothesis that white matter integrity is on the pathway between personality and cognitive health.

The effect size of the association between neuroticism and WMH was very small (about r =.02) but significant in the large UK Biobank sample (about 40000). This suggests that previous studies with roughly 200 to 600 individuals were underpowered to detect such a small effect, which may explain the mixed results in previous research (Booth et al., 2014; Byun et al., 2020; Yao et al., 2022). The effect size for neuroticism was similar in size to that of educational and economic variables, but smaller compared to smoking and vascular conditions (e.g., diabetes, hypertension, and obesity). Of interest, vascular risk factors accounted for about 40% of the association between neuroticism and WMH, but the association remained significant. This finding should be interpreted within the context of research that links neuroticism to worse health behaviors and poor cardiometabolic health. For example, individuals who score higher on neuroticism are more likely to have a sedentary lifestyle and smoke tobacco or use other addictive substances (Hakulinen et al., 2015; Kotov et al., 2010). High neuroticism is also associated with obesity, diabetes, hypertension, and worse cardiometabolic fitness (Phillips et al., 2010; Terracciano et al., 2013), including risk of stroke (Stephan et al., 2023b). Even when assessed during adolescence, neuroticism is a predictor of metabolic syndrome and worse cognitive function measured 30 years later in midlife (Sutin et al., 2022; Tanios et al., 2022). Over time, neuroticism can lead to worse cardiometabolic health, which in turn can lead to more WMH. The mediation analysis further suggests that the link between high neuroticism and poor cognition was partly mediated by WMH, independent of covariates and a vascular risk index. Thus, while vascular factors play an important role, the tendency to experience negative emotions might have other mechanisms or a direct role in WMH and cognitive function. For example, there is evidence that perceived stress (Da Silva Coelho et al., 2022; Montoliu et al., 2022) and physical fitness (Stephan et al., 2023a) are other promising pathways linking personality traits to brain health.

The findings from this study provide additional insight into the neurobiological underpinnings of the association between neuroticism and the risk for neurodegenerative conditions, particularly Alzheimer's disease and vascular dementia. The evidence that neuroticism is associated with white matter lesions is similar to findings on neuroticism and other markers of brain health (Jackson et al., 2011; Sohrabi et al., 2020). Indeed, meta-analyses that included positron emission tomography, cerebrospinal fluid, and post-mortem studies found neuroticism was associated with cortical amyloid burden and tau accumulation in the entorhinal cortex (Terracciano et al., 2022). Using blood-based assays, a recent study found neuroticism was related to evidence of neuronal injury as measured by neurofilament light (NfL)(Terracciano et al., 2023b). The same study found neuroticism associated with glial fibrillary acidic protein (GFAP), a marker sensitive to morphological and functional changes in astrocytes that occur after brain injuries or during neurodegeneration (Terracciano et al., 2023b). Importantly, the association between neuroticism and WMH, amyloid, tau, NfL, and GFAP are evident among participants without cognitive impairment, which supports the idea that neuroticism is associated with brain pathology even before clinical diagnosis. Furthermore, these findings are consistent with the hypothesis that lower neuroticism may help with brain maintenance (Nyberg et al., 2012) and improve resistance (Arenaza-Urquijo and Vemuri, 2018) against brain pathological changes (Terracciano et al., 2022).

The hypotheses of the present study were formulated from a conceptual model in which neuroticism, a relatively stable disposition that emerges early in life, is considered an antecedent of brain lesions that emerge later in life in some older adults (i.e., Neuroticism → WMH). However, the observational data examined in this study cannot determine causality. Even the mediation analyses, which are often used to test causal models, cannot determine causality in this observational study. Our results could be interpreted in the opposite direction (i.e., WMH → Neuroticism). Indeed, WMH may cause changes in neuroticism; in other words, higher neuroticism could be a sequelae of white matter lesions. This interpretation is consistent with evidence that large changes in neuroticism -and other personality traits-are observed in people with Alzheimer's disease or other dementias (Islam et al., 2019). However, neuroticism tends to increase later in the disease process and not in the preclinical stages (Terracciano et al., 2017, 2023a). The vast majority of individuals in the current sample had no clinical diagnosis of dementia, which makes the WMH → Neuroticism interpretation less likely. More longitudinal research is needed to further test mediation pathways and to better identify the timing of bidirectional influences between personality and neurodegenerative processes. Future research should also consider WMH based on visual evaluations according to the Fazekas score.

The study has limitations that should be considered. As noted above, while this study tested neuroticism as a risk factor for WMH, it is possible that more WMH could lead to increases in neuroticism, or that confounding variables (including neurological or psychiatric conditions) are responsible for this association. The observational data (particularly cross-sectional data) are a key limitation for the temporal interpretation of mediation models. Another limitation of the study is the lack of data on other major personality traits in the UK Biobank. The study is also limited to mostly white individuals from a wealthy country; more research is needed to test whether the associations would differ in contexts with fewer economic and health resources (Bond et al., 2020; Krendl and Pescosolido, 2020). While this study did not find age to

moderate the association, future studies should test these associations in older samples at greater risk of WMH.

In conclusion, this study found evidence that neuroticism is associated with higher WMH volume, an association that remained significant even after accounting for socioeconomic and vascular covariates. The study further found that WMH partially mediated the association between neuroticism and cognitive function in a large sample of middle aged and older adults.

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None.

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Author statement

AT: Conceptualization; Funding acquisition; Data curation and analyses, Writing- Original draft preparation. ARS: Conceptualization; Funding acquisition; Writing- Reviewing and Editing. XZ: Conceptualization; Data curation; Writing- Reviewing and Editing. BC, SK, YS, PPDD, SM, ML: Conceptualization; Writing- Reviewing and Editing.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2023.07.026.

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