Interactions between white matter hyperintensity progression and

STEP 1: Showing the relationship between age and memory decline

Subjects missing data for white matter hyperintensities and hippocampal volumes were dropped (n =). Next, white matter hyperintensity volume was normalised using a natural log transform. Finally, grey matter volumes are corrected by subtracting hippocampal volumes.

First, we created a "null" model, which expressed the effect of age and time on a composite memory score. Years of education and sex were also added to the model as static covariates. In this first model, baseline age represents the cross-sectional effects of age on memory, while time between follow-ups and the square of time between follow-ups represent the linear and quadratic effects of temporal progression on memory, respectively (cite).

Table 1:

	Dependent variable:
	memory
age06	-0.044^{***}
	$(-0.049, -0.038)$
sex1	0.118^{**}
	(0.018, 0.219)
educationyears	0.134^{***}
	(0.105, 0.163)
time	-0.175^{***}
	$(-0.194, -0.156)$
timesq	0.017^{***}
	(0.015, 0.020)
Constant	1.481^{***}
	(0.962, 2.001)
Observations	1,147
Log Likelihood	−856.868
Akaike Inf. Crit.	1,733.735
Bayesian Inf. Crit.	1,784.184
Note:	*p<0.1; **p<0.05; ***p<0.01

We then adopted a data-driven approach to determine the role of WMH and HV in contributing to memory deficits. Using the null model as a baseline, three successive models were created: one with only the effects of WMH, a second with only the effects of HV, and a third with the simulatenous effects of WMH and HV.

These three models, along with the null model, were then compared to see which model best explained the data. Since the random effect is identical across all models, the fixed effects are compared. Also all other models can be seen as restricted cases of the final model.

In order to facilitate comparisons between models with different fixed effects, models were fit by minimising the negative log-likelihood. All models were then compared using a one-way ANOVA.

Both models with WMH only and HV only provided significantly better fit in comparison to the null model. The model with HV alone fit better than the model with WMH alone. Importantly, however, the model with both WMH and HV provided the best fit to the data. As such, this model was re-fit using REML to obtain strong effects for standardised estimates.

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Table 2:

	Df	AIC	BIC	logLik	deviance	Chisq	Chi Df	Pr(>Chisq)
model1	10	1,733.735	1,784.184	-856.868	1,713.735			
model2	12	1,708.023	1,768.562	-842.012	1,684.023	29.712	2	0.00000
model3	12	1,668.242	1,728.781	-822.121	1,644.242	39.781	0	0
model5	14	1,658.078	1,728.707	-815.039	1,630.078	14.164	2	0.001
model4	15	1,644.448	1,720.122	-807.224	1,614.448	15.630	1	0.0001

We then compared this model with several alternative competing models to determine the specificity of the effect.

First, we wanted to show that the effect of hippocampal atrophy was not part of general grey matter atrophy.

Next, we wanted to show that the effect is specific for memory, rather than general cognition.

Importantly, indices such as the BIC penalise the addition of further parameters, and are thus more sensitive to overfitting.

Table 3: Fixed effects results

	Dependent variable:				
	Null	WMH only	Memory HV only	WMH and HV	Full
	(1)	(2)	(3)	(4)	(5)
Age (years)	−.044*** (−.049, −.038)	−.040*** (−.047, −.034)	−.035*** (−.042, −.029)	−.033*** (−.041, −.026)	−.032*** (−.039, −.025
Sex	.118* (.018, .219)	.126* (.026, .227)	.052 (−.052, .156)	.062 (−.043, .167)	.072 (−.032, .176)
Education (years)	.134*** (.105, .163)	.132*** (.104, .161)	.133*** (.104, .161)	.131*** (.103, .160)	.136*** (.108, .165)
Time to follow-up (linear)	−.175*** (−.194, −.156)	−.182*** (−.201, −.162)	−.331*** (−.384, −.277)	−.312*** (−.366, −.258)	−.273*** (−.330, −.215
Time to follow-up (quadratic)	.017*** (.015, .020)	.021*** (.019, .024)	.018*** (.016, .020)	.020*** (.018, .023)	.019*** (.017, .022)
WMH		−.014 (−.053, .026)		−.015 (−.054, .025)	−.504*** (−.748, −.259
WMH progression		−.002*** (−.002, −.001)		−.001*** (−.002, −.0005)	−.001* (−.001, −.000
HV			.062* (.003, .120)	.064* (.005, .123)	−.018 (−.089, .053)
Hippocampal atrophy			.021*** (.015, .028)	.018*** (.012, .025)	.013*** (.006, .020)
WMH * HV interaction					.064*** (.032, .095)
Observations	1,147	1,147	1,147	1,147	1,147
Log Likelihood	−856.868	−842.012	−822.121	−815.039	−807.224
Akaike Inf. Crit.	1,733.735	1,708.023	1,668.242	1,658.078	1,644.448
Bayesian Inf. Crit.	1,784.184	1,768.562	1,728.781	1,728.707	1,720.122
Note:					*p<0.05; **p<0.01; ***p<0.0

Table 4:

	Df	AIC	BIC	logLik	deviance	Chisq	Chi Df	Pr(>Chisq)
model4	15	1,644.448	1,720.122	-807.224	1,614.448			
model4a	15	1,668.730	1,744.404	-819.365	1,638.730	0	0	1
model4b	15	1,366.489	1,442.163	-668.245	1,336.489	302.241	0	0