Memory decline in elderly with cerebral small vessel disease explained by temporal interactions between white matter hyperintensities and hippocampal atrophy

1. Showing the relationship between age and memory decline

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.

Table 1:

	Dependent variable:
	memory
Baseline age (years)	-0.044^{***}
	$(-0.049, -0.038)$
Sex	0.118^{**}
	$(0.018, 0.219)$
Education (years)	0.134^{***}
	$(0.105, 0.163)$
Time to follow-up (linear)	-0.175^{***}
	$(-0.194, -0.156)$
Time to follow-up (quadratic)	0.017^{***}
	$(0.015, 0.020)$
Observations	1,147
Log Likelihood	−856.868
Akaike Inf. Crit.	1,733.735
Bayesian Inf. Crit.	1,784.184
Note:	$^{*}p<0.1$; $^{**}p<0.05$; $^{***}p<0.01$

2. Examining the interaction between WMH and HV in explaining memory decline

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.

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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
model4	15	1,644.448	1,720.122	-807.224	1,614.448	29.794	3	0.00000

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Table 3:

	Df	AIC	BIC	logLik	deviance	Chisq	Chi Df	Pr(>Chisq)
model5	14	1,658.078	1,728.707	-815.039	1,630.078			
model4	15	1,644.448	1,720.122	-807.224	1,614.448	15.630	1	0.0001

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.

3. Memory examined separately as long-term memory (i.e. immediate and delayed memory) and working memory

Working memory and long-term memory were examined separately, as we have indications that they are affected differently by WMH and HV [1].

3a. Working memory

Working memory and long-term memory were examined separately.

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3b. Immediate memory

Working memory and long-term memory were examined separately.

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[1] Charlton RA, Barrick TR, Markus HS, Morris RG. The relationship between episodic long-term memory and white matter integrity in normal aging. Neuropsychologia 2010; 48: 114-22.

Table 4: Fixed effects results

	Dependent variable:			
	Memory			
	Null	WMH only	HV only	Full
	(1)	(2)	(3)	(4)
Baseline age (years)	$-.044^{***}$	$-.040^{***}$	$-.035^{***}$	$-.032^{***}$
	$(-.049, -.038)$	$(-.047, -.034)$	$(-.042, -.029)$	$(-.039, -.025)$
Sex	$.118^{*}$	$.126^{*}$	.052	.072
	(.018, .219)	(.026, .227)	$(-.052, .156)$	$(-.032, .176)$
Education (years)	$.134^{***}$	$.132^{***}$	$.133^{***}$	$.136^{***}$
	(.105, .163)	(.104, .161)	(.104, .161)	(.108, .165)
Time to follow-up (linear)	$-.175^{***}$	$-.182^{***}$	$-.331^{***}$	$-.273^{***}$
	$(-.194, -.156)$	$(-.201, -.162)$	$(-.384, -.277)$	$(-.330, -.215)$
Time to follow-up (quadratic)	$.017^{***}$	$.021^{***}$	$.018^{***}$	$.019^{***}$
	(.015, .020)	(.019, .024)	(.016, .020)	(.017, .022)
WMH		$-.014$		$-.504^{***}$
		$(-.053, .026)$		$(-.748, -.259)$
WMH progression		$-.002^{***}$		$-.001^{*}$
		$(-.002, -.001)$		$(-.001, -.0001)$
HV			$.062^{*}$	$-.018$
			(.003, .120)	$(-.089, .053)$
Hippocampal atrophy			$.021^{***}$	$.013^{***}$
			(.015, .028)	(.006, .020)
WMH * HV interaction				$.064^{***}$
				(.032, .095)
Observations	1,147	1,147	1,147	1,147
Log Likelihood	-856.868	-842.012	-822.121	-807.224
Akaike Inf. Crit.	1,733.735	1,708.023	1,668.242	1,644.448
Bayesian Inf. Crit.	1,784.184	1,768.562	1,728.781	1,720.122
Note:				*p<0.05; **p<0.01; ***p<0.001

Table 5:

	Df	AIC	BIC	logLik	deviance	Chisq	Chi Df	Pr(>Chisq)
wm.model5	14	2, 386.847	2, 457.291	-1, 179.423	2, 358.847			
wm.model4	15	2, 379.532	2, 455.009	-1, 174.766	2, 349.532	9.314	1	0.002

Table 6: Fixed effects results

	Dependent variable:			
	Working Memory			
	Null	WMH only	HV only	Full
	(1)	(2)	(3)	(4)
Baseline age (years)	$-.046^{***}$	$-.043^{***}$	$-.041^{***}$	$-.038^{***}$
	$(-.054, -.038)$	$(-.052, -.034)$	$(-.051, -.032)$	$(-.048, -.028)$
Sex	$.191^{**}$	$.198^{**}$	$.152^{*}$	$.173^{*}$
	(.057, .324)	(.065, .331)	(.013, .292)	(.034, .313)
Education (years)	$.132^{***}$	$.131^{***}$	$.131^{***}$	$.135^{***}$
	(.094, .170)	(.092, .169)	(.093, .169)	(.097, .173)
Time to follow-up (linear)	$-.092^{***}$	$-.095^{***}$	$-.171^{***}$	$-.119^{**}$
	$(-.119, -.064)$	$(-.123, -.068)$	$(-.247, -.096)$	$(-.200, -.038)$
Time to follow-up (quadratic)	.003	$.005^{**}$	.003	.004
	$(-.001, .006)$	(.001, .009)	$(-.0004, .006)$	$(-.0001, .007)$
WMH		$-.016$		$-.534^{**}$
		$(-.070, .038)$		$(-.869, -.199)$
WMH progression		$-.001^{*}$		$-.0004$
		$(-.002, -.0002)$		$(-.001, .0005)$
HV			.029	$-.057$
			$(-.052, .111)$	$(-.156, .042)$
Hippocampal atrophy			$.011^{*}$	.004
			(.002, .020)	$(-.006, .014)$
WMH * HV interaction				$.067^{**}$
				(.024, .111)
Observations	1,132	1,132	1,132	1,132
Log Likelihood	−1,186.406	−1,182.732	−1,181.520	−1,174.766
Akaike Inf. Crit.	2,392.813	2,389.464	2,387.039	2,379.532
Bayesian Inf. Crit.	2,443.130	2,449.845	2,447.420	2,455.009
Note:				*p<0.05; **p<0.01; ***p<0.001

Table 7:

	Df	AIC	BIC	logLik	deviance	Chisq	Chi Df	Pr(>Chisq)
im.model5	14	2, 120.532	2, 191.148	-1, 046.266	2, 092.532			
im.model4	15	2, 113.184	2, 188.844	-1, 041.592	2, 083.184	9.348	1	0.002

Table 8: Fixed effects results

	Dependent variable:			
	Immediate Memory			
	Null	WMH only	HV only	Full
	(1)	(2)	(3)	(4)
Baseline age (years)	$-.042^{***}$	$-.039^{***}$	$-.033^{***}$	$-.030^{***}$
	($-.049$, $-.035$)	($-.046$, $-.031$)	($-.041$, $-.025$)	($-.039$, $-.021$)
Sex	.114	$.121^{*}$	.046	.065
	($-.003$, .231)	(.004, .239)	($-.075$, .167)	($-.057$, .186)
Education (years)	$.147^{***}$	$.145^{***}$	$.146^{***}$	$.149^{***}$
	(.113, .181)	(.111, .179)	(.112, .179)	(.116, .183)
Time to follow-up (linear)	$-.240^{***}$	$-.247^{***}$	$-.430^{***}$	$-.375^{***}$
	($-.265$, $-.215$)	($-.272$, $-.222$)	($-.496$, $-.364$)	($-.446$, $-.305$)
Time to follow-up (quadratic)	$.028^{***}$	$.032^{***}$	$.028^{***}$	$.030^{***}$
	(.025, .031)	(.028, .035)	(.025, .031)	(.027, .033)
WMH		$-.011$		$-.468^{**}$
		($-.058$, .036)		($-.761$, $-.175$)
WMH progression		$-.002^{***}$		$-.001^{*}$
		($-.003$, $-.001$)		($-.002$, $-.00003$)
HV			.050	$-.021$
			($-.020$, .121)	($-.107$, .064)
Hippocampal atrophy			$.026^{***}$	$.018^{***}$
			(.018, .034)	(.010, .027)
WMH * HV interaction				$.059^{**}$
				(.021, .097)
Observations	1,146	1,146	1,146	1,146
Log Likelihood	$-1,082.382$	$-1,070.884$	$-1,051.291$	$-1,041.592$
Akaike Inf. Crit.	2,184.764	2,165.767	2,126.583	2,113.184
Bayesian Inf. Crit.	2,235.204	2,226.295	2,187.111	2,188.844

Note: *p<0.05; **p<0.01; ***p<0.001

3c. Delayed memory

Working memory and long-term memory were examined separately.

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Table 9:

	Df	AIC	BIC	logLik	deviance	Chisq	Chi Df	Pr(>Chisq)
dm.model5	14	2,140.403	2,211.008	-1,056.202	2,112.403			
dm.model4	15	2,131.685	2,207.332	-1,050.842	2,101.685	10.719	1	0.001

4. Determine the specificity of the effect

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

4.1 Grey matter atrophy

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

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4.2 Global cognition

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

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4.3 Psychomotor speed

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

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4.4 Executive function

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

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Table 10: Fixed effects results

	Dependent variable:			
	Delayed Memory			
	Null	WMH only	HV only	Full
	(1)	(2)	(3)	(4)
Baseline age (years)	$-.045^{***}$	$-.042^{***}$	$-.034^{***}$	$-.030^{***}$
	$(-.052, -.038)$	$(-.050, -.033)$	$(-.042, -.026)$	$(-.039, -.021)$
Sex	.081	.091	$-.008$	.016
	$(-.041, .204)$	$(-.032, .214)$	$(-.133, .118)$	$(-.110, .142)$
Education (years)	$.122^{***}$	$.120^{***}$	$.121^{***}$	$.125^{***}$
	(.087, .158)	(.085, .156)	(.086, .156)	(.090, .159)
Time to follow-up (linear)	$-.194^{***}$	$-.201^{***}$	$-.370^{***}$	$-.310^{***}$
	$(-.219, -.169)$	$(-.226, -.176)$	$(-.435, -.304)$	$(-.381, -.240)$
Time to follow-up (quadratic)	$.023^{***}$	$.027^{***}$	$.023^{***}$	$.025^{***}$
	(.020, .025)	(.023, .030)	(.020, .026)	(.021, .028)
WMH		$-.014$		$-.511^{***}$
		$(-.063, .035)$		$(-.811, -.212)$
WMH progression		$-.002^{***}$		$-.001^{*}$
		$(-.003, -.001)$		$(-.002, -.0001)$
HV			$.089^{*}$	.010
			(.016, .161)	$(-.079, .098)$
Hippocampal atrophy			$.024^{***}$	$.016^{***}$
			(.016, .032)	(.008, .025)
WMH * HV interaction				$.065^{**}$
				(.026, .103)
Observations	1,145	1,145	1,145	1,145
Log Likelihood	−1,097.762	−1,084.412	−1,062.280	−1,050.842
Akaike Inf. Crit.	2,215.523	2,192.823	2,148.560	2,131.685
Bayesian Inf. Crit.	2,265.955	2,253.341	2,209.078	2,207.332
Note:				*p<0.05; **p<0.01; ***p<0.001

Table 11:

	Df	AIC	BIC	logLik	deviance	Chisq	Chi Df	Pr(>Chisq)
model4	15	1,644.448	1,720.122	-807.224	1,614.448			
gm.model4	15	1,668.730	1,744.404	-819.365	1,638.730	0	0	1

Table 12:

	Df	AIC	BIC	logLik	deviance	Chisq	Chi Df	Pr(>Chisq)
gm.model5	14	$1,672.722$	$1,743.351$	-822.361	$1,644.722$			
gm.model4	15	$1,668.730$	$1,744.404$	-819.365	$1,638.730$	5.992	1	0.014

Table 13:

	Df	AIC	BIC	logLik	deviance	Chisq	Chi Df	Pr(>Chisq)
gm.m5	13	$1,744.544$	$1,810.127$	-859.272	$1,718.544$			
gm.m4	14	$1,742.865$	$1,813.494$	-857.433	$1,714.865$	3.678	1	0.055

Table 14: Fixed effects results

	Dependent variable:			
	Memory			
	Null	WMH only	GMV only	Full
	(1)	(2)	(3)	(4)
Baseline age (years)	$-.044^{***}$	$-.040^{***}$	$-.038^{***}$	$-.036^{***}$
	$(-.049, -.038)$	$(-.047, -.034)$	$(-.045, -.031)$	$(-.043, -.029)$
Sex	$.118^{*}$	$.126^{*}$	$.065$	$.081$
	$(.018, .219)$	$(.026, .227)$	$(-.041, .171)$	$(-.026, .187)$
Education (years)	$.134^{***}$	$.132^{***}$	$.132^{***}$	$.133^{***}$
	$(.105, .163)$	$(.104, .161)$	$(.103, .161)$	$(.104, .162)$
Time to follow-up (linear)	$-.175^{***}$	$-.182^{***}$	$-.472^{***}$	$-.395^{***}$
	$(-.194, -.156)$	$(-.201, -.162)$	$(-.555, -.389)$	$(-.488, -.303)$
Time to follow-up (quadratic)	$.017^{***}$	$.021^{***}$	$.019^{***}$	$.020^{***}$
	$(.015, .020)$	$(.019, .024)$	$(.017, .021)$	$(.018, .023)$
WMH		$-.014$		$-.500^{*}$
		$(-.053, .026)$		$(-.888, -.112)$
WMH progression		$-.002^{***}$		$-.001^{*}$
		$(-.002, -.001)$		$(-.001, -.00004)$
GMV			$.0004$	$-.001$
			$(-.001, .002)$	$(-.002, .001)$
GM atrophy			$.0005^{***}$	$.0004^{***}$
			$(.0004, .001)$	$(.0002, .001)$
WMH * GMV interaction				$.001^{*}$
				$(.0002, .001)$
Observations	1,147	1,147	1,147	1,147
Log Likelihood	−856.868	−842.012	−827.147	−819.365
Akaike Inf. Crit.	1,733.735	1,708.023	1,678.294	1,668.730
Bayesian Inf. Crit.	1,784.184	1,768.562	1,738.833	1,744.404
Note:				*p<0.05; **p<0.01; ***p<0.001

Table 15:

	Df	AIC	BIC	logLik	deviance	Chisq	Chi Df	Pr(>Chisq)
ci.model5	14	1,227.553	1,298.182	-599.777	1,199.553			
ci.model4	15	1,215.282	1,290.956	-592.641	1,185.282	14.271	1	0.0002

Table 16: Fixed effects results

	Dependent variable:			
	Cognitive Index			
	Null	WMH only	HV only	Full
	(1)	(2)	(3)	(4)
Baseline age (years)	$-.043^{***}$	$-.039^{***}$	$-.034^{***}$	$-.030^{***}$
	$(-.048, -.037)$	$(-.045, -.033)$	$(-.040, -.027)$	$(-.037, -.024)$
Sex	$.115^{*}$	$.126^{**}$	.045	.067
	(.022, .209)	(.033, .219)	$(-.052, .143)$	$(-.030, .163)$
Education (years)	$.166^{***}$	$.164^{***}$	$.164^{***}$	$.167^{***}$
	(.139, .192)	(.137, .190)	(.138, .191)	(.140, .193)
Time to follow-up (linear)	$-.125^{***}$	$-.132^{***}$	$-.275^{***}$	$-.224^{***}$
	$(-.140, -.111)$	$(-.146, -.117)$	$(-.317, -.233)$	$(-.270, -.178)$
Time to follow-up (quadratic)	$.010^{***}$	$.014^{***}$	$.011^{***}$	$.012^{***}$
	(.009, .012)	(.012, .016)	(.009, .012)	(.010, .014)
WMH		$-.023$		$-.431^{***}$
		$(-.058, .012)$		$(-.644, -.218)$
WMH progression		$-.002^{***}$		$-.001^{**}$
		$(-.002, -.001)$		$(-.001, -.0002)$
HV			$.072^{**}$	.002
			(.021, .123)	$(-.060, .065)$
Hippocampal atrophy			$.020^{***}$	$.013^{***}$
			(.015, .025)	(.008, .019)
WMH * HV interaction				$.053^{***}$
				(.026, .080)
Observations	1,147	1,147	1,147	1,147
Log Likelihood	-658.432	-638.823	-609.023	-592.641
Akaike Inf. Crit.	1,336.864	1,301.647	1,242.046	1,215.282
Bayesian Inf. Crit.	1,387.313	1,362.185	1,302.585	1,290.956
Note:				*p<0.05; **p<0.01; ***p<0.001

Table 17:

	Df	AIC	BIC	logLik	deviance	Chisq	Chi Df	Pr(>Chisq)
ps.model5	14	1,653.340	1,723.859	-812.670	1,625.340			
ps.model4	15	1,651.528	1,727.083	-810.764	1,621.528	3.812	1	0.051

Table 18: Fixed effects results

	Dependent variable:			
	Psychomotor Speed			
	Null	WMH only	HV only	Full
	(1)	(2)	(3)	(4)
Baseline age (years)	$-.045^{***}$	$-.040^{***}$	$-.036^{***}$	$-.031^{***}$
	$(-.052, -.039)$	$(-.047, -.032)$	$(-.043, -.028)$	$(-.039, -.023)$
Sex	$.161^{**}$	$.175^{**}$	.082	.107
	(.048, .273)	(.063, .287)	$(-.035, .200)$	$(-.010, .224)$
Education (years)	$.171^{***}$	$.168^{***}$	$.170^{***}$	$.169^{***}$
	(.138, .203)	(.136, .200)	(.137, .202)	(.137, .201)
Time to follow-up (linear)	$-.087^{***}$	$-.091^{***}$	$-.187^{***}$	$-.156^{***}$
	$(-.104, -.071)$	$(-.108, -.075)$	$(-.240, -.135)$	$(-.214, -.098)$
Time to follow-up (quadratic)	$.004^{***}$	$.007^{***}$	$.005^{***}$	$.006^{***}$
	(.002, .006)	(.005, .009)	(.003, .006)	(.004, .008)
WMH		$-.051^{*}$		$-.305^{*}$
		$(-.094, -.009)$		$(-.564, -.047)$
WMH progression		$-.001^{***}$		$-.001$
		$(-.002, -.0005)$		$(-.001, .0001)$
HV			$.093^{**}$	.043
			(.030, .156)	$(-.033, .120)$
Hippocampal atrophy			$.014^{***}$	$.010^{**}$
			(.008, .020)	(.003, .017)
WMH * HV interaction				$.033^{*}$
				(.0001, .067)
Observations	1,138	1,138	1,138	1,138
Log Likelihood	−842.978	−831.142	−819.337	−810.764
Akaike Inf. Crit.	1,705.957	1,686.284	1,662.675	1,651.528
Bayesian Inf. Crit.	1,756.327	1,746.729	1,723.119	1,727.083
Note:				*p<0.05; **p<0.01; ***p<0.001

Table 19:

	Df	AIC	BIC	logLik	deviance	Chisq	Chi Df	Pr(>Chisq)
ef.model5	14	1,646.107	1,716.735	-809.053	1,618.107			
ef.model4	15	1,636.964	1,712.637	-803.482	1,606.964	11.143	1	0.001

Table 20: Fixed effects results

	Dependent variable:			
	Executive function			
	Null	WMH only	HV only	Full
	(1)	(2)	(3)	(4)
Baseline age (years)	$-.038^{***}$	$-.035^{***}$	$-.032^{***}$	$-.029^{***}$
	$(-.044, -.033)$	$(-.042, -.029)$	$(-.039, -.025)$	$(-.036, -.021)$
Sex	.037	.046	$-.017$	.003
	$(-.063, .136)$	$(-.054, .145)$	$(-.122, .087)$	$(-.101, .108)$
Education (years)	$.181^{***}$	$.179^{***}$	$.179^{***}$	$.182^{***}$
	(.152, .209)	(.151, .208)	(.151, .208)	(.154, .211)
Time to follow-up (linear)	$-.038^{***}$	$-.044^{***}$	$-.180^{***}$	$-.126^{***}$
	$(-.057, -.018)$	$(-.064, -.024)$	$(-.231, -.128)$	$(-.181, -.070)$
Time to follow-up (quadratic)	.001	$.004^{**}$	.001	$.003^{*}$
	$(-.002, .003)$	(.002, .007)	$(-.001, .003)$	(.0002, .005)
WMH		$-.013$		$-.429^{***}$
		$(-.052, .026)$		$(-.674, -.184)$
WMH progression		$-.002^{***}$		$-.001^{**}$
		$(-.002, -.001)$		$(-.001, -.0002)$
HV			.044	$-.024$
			$(-.014, .102)$	$(-.095, .047)$
Hippocampal atrophy			$.019^{***}$	$.012^{***}$
			(.013, .025)	(.005, .019)
WMH * HV interaction				$.054^{***}$
				(.022, .085)
Observations	1,147	1,147	1,147	1,147
Log Likelihood	−844.436	−829.147	−816.935	−803.482
Akaike Inf. Crit.	1,708.873	1,682.293	1,657.870	1,636.964
Bayesian Inf. Crit.	1,759.322	1,742.832	1,718.409	1,712.637
Note:				*p<0.05; **p<0.01; ***p<0.001