



Brain volumes in late life: gender, hormone treatment, and estrogen receptor variants.

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Table 1. Characteristics of the 582 participants according to gender and women's use of HT.

Characteristic	Males (N=287)	Females (N=295)		
		Never HT	Past HT	Current HT
Median (Interquartile range: 25 th – 75 th percentile)				
Age (years)	71 (68 to 74) [†]	71 (68 to 75) [‡]	70 (68 to 72)	68 (67 to 71)
Body Mass Index (kg/m ²)	25.6 (23.7 to 27.4) [†]	24.1 (22.0 to 26.7) [‡]	23.9 (21.6 to 26.3)	23.2 (21.1 to 25.5)
	N (%)	N (%)	N (%)	N (%)
≥ 12 years of education	126 (43.9) [†]	45 (26.0) [‡]	12 (20.0)	29 (46.8)
Living alone	17 (5.9) [†]	59 (34.1)	15 (25.0)	14 (22.6)
High alcohol consumption (≥ 24 g each day)	100 (34.8) [†]	9 (5.2)	4 (6.6)	5 (8.1)
Smoking history (10 pack year)	98 (34.2) [†]	32 (18.5)	15 (25.0)	15 (24.2)
Current depressive symptoms (CES-D ≥16)	58 (20.2) [†]	58 (33.5)	24 (40.0)	17 (27.4)
Lifetime major depressive disorder ^a	37 (14.0) [†]	54 (34.4)	25 (45.5)	28 (46.7)
Low global cognitive function (MMSE≤24)	15 (5.2) [†]	21 (12.1)	6 (10.0)	3 (4.8)
History of cardiovascular disease	58 (20.2)	36 (20.8) [‡]	8 (13.3)	6 (9.7)
Hypertension (≥ 160/95mm Hg or treatment)	138 (48.1)	86 (49.7) [‡]	27 (45.0)	17 (27.4)
Diabetes (fasting glucose ≥ 7.0mmol/l or treatment)	37 (12.9) [†]	12 (6.9) [‡]	1 (1.7)	0 (0.0)

Hypercholesterolemia	79 (27.6) [†]	67 (38.7)	25 (41.7)	21 (33.9)
Anticholinergic medication	7 (2.4) [†]	9 (5.2) [*]	2 (3.3)	9 (14.5)
Current user of ≥3 medications	94 (32.8) [†]	72 (44.5) [†]	20 (33.3)	20 (32.3)
Carrier of the <i>APOE</i> ε4 allele	61 (21.3)	42 (24.3)	14 (23.3)	10 (16.1)
Median (Interquartile range: 25th – 75th percentile)				
Volume of grey matter, cm ³	684 (643 to 729)	631 (598 to 662)	630 (608 to 661)	623 (594 to 659)
Ratio of grey matter to ICV	54.5 (53.4 to 56.4)	55.2 (53.8 to 56.9)	55.9 (54.6 to 57.9)	54.8 (53.2 to 55.9)
Volume of white matter volume, cm ³	374 (346 to 407)	339 (315 to 362)	334 (314 to 360)	342 (327 to 365)
Ratio of white matter to ICV	29.8 (28.5 to 31.4)	29.6 (28.3 to 31.0)	29.3 (28.3 to 30.3)	30.4 (28.7 to 31.4)
Total volume of hippocampus, mm ³	5964 (5510 to 6481)	5653 (5109 to 6011)	5619 (5136 to 6114)	5572 (5231 to 6048)
Ratio of hippocampus to ICV	4.7 (4.3 to 5.3)	4.9 (4.5 to 5.3)	5.0 (4.2-5.3)	4.9 (4.5-5.4)
Midsagittal total corpus callosum area, mm ²	609 (546 to 670)	591 (524 to 651)	574 (534 to 652)	596 (527 to 671)
Ratio of corpus callosum to ICV	0.48 (0.43 to 0.54)	0.52 (0.47 to 0.57)	0.51 (0.46 to 0.58)	0.52 (0.46 to 0.60)
Total volume of WML, cm ³	0.8 (0.3 to 3.2)	0.60 (0.2 to 2.1)	0.80 (0.2 to 2.4)	0.45 (0.2 to 2.1)
Volume of WML transformed (log ₁₀)	-0.09 (-0.51 to 0.51)	-0.21 (-0.68 to 0.32)	-0.09 (-0.68 to 0.39)	-0.34 (-0.68 to 0.32)
	N (%)	N (%)	N (%)	N (%)
Participants with no detectable WML	10 (3.5)	11 (6.4)	3 (5.0)	2 (3.2)

^aData were missing for 23 men and women. [†]Significantly different between genders at $p \leq 0.10$. [‡]Significantly different between women according to their use or not of HT at $p \leq 0.10$.

Table 2. Linear regression models for the association between brain measures^a and gender or use of HT.

Model	N	Grey Matter	White Matter	Hippocampus	Corpus Callosum	White Matter Lesions
		Beta (SE), p	Beta (SE), p	Beta (SE), p	Beta (SE), p	Beta (SE), p
<u>Age-adjusted</u>						
Women, never HT	173	1	1	1	1	1
Women, past HT	60	0.40 (0.38), 0.28	-0.44 (0.30), 0.14	0.02 (0.10), 0.83	-0.01 (0.01), 0.34	0.12 (0.11), 0.28
Women, current HT	62	-0.94 (0.38), 0.01*	0.18 (0.30), 0.54	-0.06 (0.10), 0.60	-0.003 (0.01), 0.84	0.08 (0.11), 0.51
Men	287	-0.68 (0.24), 0.005**	0.23 (0.19), 0.22	-0.09 (0.06), 0.16	-0.03 (0.01), 0.001**	-0.02 (0.008), 0.78
<u>Multivariable-adjusted^b</u>						
Women, never HT	173	1	1	1	1	1
Women, past HT	60	0.38 (0.37), 0.31	-0.47, (0.30), 0.11	0.007 (0.10), 0.94	-0.01 (0.01), 0.30	0.14 (0.11), 0.22
Women, current HT	62	-1.11 (0.38), 0.003**	0.32 (0.30), 0.29	-0.09 (0.10), 0.39	-0.003 (0.01), 0.84	0.13 (0.11), 0.24
Men	287	-0.75 (0.24), 0.002**	0.28 (0.20), 0.15	-0.10 (0.07), 0.11	-0.03 (0.01), 0.001**	0.008 (0.08), 0.92

^aAll brain measures are given as a percentage of total intracranial volume (ICV), except for the volume of white matter lesions, which were adjusted for the volume of white matter.

^bAdjusted for age, educational level, cardiovascular disease, hypertension and number of medications

*p<0.05; **p≤0.005

Table 3. Linear regression models for the multivariable-adjusted association^a between ESR polymorphisms and brain measures^b in women.

Model	N	Grey Matter	White Matter	Hippocampus	Corpus Callosum	White Matter Lesions
		Beta (SE), p-value	Beta (SE), p-value	Beta (SE), p	Beta (SE), p	Beta (SE), p-value
<u>ESR1</u>						
<i>rs2234693</i> : C allele	205	1	1	1	1	1
TT	90	-0.29 (0.33), 0.38	0.21 (0.24), 0.38	0.10 (0.08), 0.22	0.006 (0.01), 0.54	0.26 (0.10), 0.008*
<i>rs9340799</i> : G allele	171	1	1	1	1	1
AA	124	-0.16 (0.31), 0.60	0.26 (0.22), 0.24	0.11 (0.07), 0.14	0.0003 (0.01), 0.98	0.13 (0.09), 0.18
<u>ESR2</u>						
<i>rs1271572</i> : T allele	206	1	1	1	1	1
GG	89	-0.20 (0.33), 0.55	-0.09 (0.24), 0.72	-0.001 (0.08), 0.99	-0.003 (0.01), 0.81	0.01 (0.10), 0.91
<i>rs4986938</i> : A allele	202	1	1	1	1	1
GG	93	0.48 (0.33), 0.15	0.09 (0.24), 0.73	0.12 (0.08), 0.12	0.01 (0.01), 0.31	-0.04 (0.10), 0.66
<i>rs1256049</i> : A allele	26	1	1	1	1	1
GG	269	-0.26 (0.55), 0.64	-0.24 (0.40), 0.55	0.11 (0.13), 0.41	-0.02 (0.02), 0.24	-0.03 (0.17), 0.86

^aAll brain measures are given as a percentage of total intracranial brain volume, except for the volume of white matter lesions, which were adjusted for the volume of white matter.

^bAdjusted for age, educational level, cardiovascular disease, hypertension and number of medications.

* $p < 0.05$; ** $p \leq 0.005$

Table 4. Linear regression models for the association between ESR1 variants and white matter lesions^a in women, stratified by HT.

	Hormone Treatment					
	Never		Past		Current	
	N	Beta (SE), p-value	N	Beta (SE), p-value	N	Beta (SE), p-value
<u>Age-adjusted</u>						
<i>rs2234693</i> : C allele	53	1	43	1	42	1
TT	120	0.40 (0.13), 0.002**	17	-0.42 (0.21), 0.08	20	0.35 (0.21), 0.10
<i>rs9340799</i> : G allele	71	1	27	1	26	1
AA	102	0.21 (0.12), 0.09	33	-0.47 (0.21), 0.03*	36	0.42 (0.19), 0.03*
<u>Multivariable-adjusted^b</u>						
<i>rs2234693</i> : C allele	53	1	43	1	42	1
TT	120	0.38 (0.13), 0.003**	17	-0.18 (0.25), 0.48	20	0.43 (0.20), 0.04*
<i>rs9340799</i> : G allele	71	1	27	1	26	1
AA	102	0.19 (0.12), 0.12	33	-0.30 (0.21), 0.17	36	0.45 (0.19), 0.02*

^aAdjusted for the volume of white matter.

^bAdjusted for age, educational level, cardiovascular disease, hypertension and number of medications.

*p<0.05; **p≤0.005

Supplementary Table 1. Linear regression model for the association between ESR1 polymorphisms and brain measures^a in men.

Model	N	Grey Matter	White Matter	Hippocampus	Corpus Callosum	White Matter Lesions
		Beta (SE), p	Beta (SE), p	Beta (SE), p	Beta (SE), p	Beta (SE), p
<u>Age-adjusted</u>						
<i>rs2234693</i> : C allele	79	1	1	1	1	1
TT	208	-0.33 (0.33), 0.31	-0.04 (0.28), 0.89	0.05 (0.10), 0.60	-0.02 (0.01), 0.07	-0.01 (0.10), 0.91
<i>rs9340799</i> : G allele	114	1	1	1	1	1
AA	173	-0.31 (0.30), 0.30	0.18 (0.26), 0.47	0.05 (0.09), 0.58	-0.01 (0.01), 0.36	-0.008 (0.09), 0.93
<u>Multivariable-adjusted^b</u>						
<i>rs2234693</i> : C allele	79	1	1	1	1	1
TT	208	-0.35 (0.32), 0.28	-0.04 (0.28), 0.89	0.06 (0.09), 0.50	-0.02 (0.01), 0.07	-0.007 (0.10), 0.94
<i>rs9340799</i> : G allele	114	1	1	1	1	1
AA	173	-0.36 (0.30), 0.23	0.20 (0.26), 0.45	0.05 (0.09), 0.60	-0.01 (0.01), 0.36	0.004 (0.09), 0.97

^aAll brain measures are given as a percentage of total intracranial brain volume, except for the volume of white matter lesions, which were adjusted for the volume of white matter.

^bAdjusted for age, educational level, cardiovascular disease, hypertension and number of medications

Supplementary Table 2. Linear regression model for the association between ESR2 polymorphisms and brain measures^a in men.

Model	N	Grey Matter	White Matter	Hippocampus	Corpus Callosum	White Matter Lesions
		Beta (SE), p	Beta (SE), p	Beta (SE), p	Beta (SE), p	Beta (SE), p
<u>Age-adjusted</u>						
<i>rs1271572</i> : T allele	196	1	1	1	1	1
GG	91	-0.09 (0.31), 0.79	0.16 (0.27), 0.55	0.01 (0.09), 0.90	0.00 (0.01), 0.95	-0.06 (0.09), 0.53
<i>rs4986938</i> : A allele	176	1	1	1	1	1
GG	111	0.36 (0.30), 0.23	0.02 (0.26), 0.93	0.09 (0.09), 0.30	0.00 (0.01), 0.99	-0.05 (0.09), 0.57
<i>rs1256049</i> : A allele	23	1	1	1	1	1
GG	264	-0.77 (0.57), 0.19	0.49 (0.50), 0.33	-0.16 (0.18), 0.38	-0.02 (0.02), 0.29	-0.23 (0.17), 0.18
<u>Multivariable-adjusted^b</u>						
<i>rs1271572</i> : T allele	196	1	1	1	1	1
GG	91	-0.18 (0.31), 0.56	0.16 (0.30), 0.56	-0.02 (0.09), 0.82	0.00 (0.01), 0.99	-0.04 (0.09), 0.70
<i>rs4986938</i> : A allele	176	1	1	1	1	1
GG	111	0.43 (0.30), 0.16	0.02 (0.26), 0.93	0.09 (0.09), 0.27	0.00 (0.01), 0.98	-0.07 (0.09), 0.44
<i>rs1256049</i> : A allele	23	1	1	1	1	1
GG	264	-0.68 (0.57), 0.23	0.51 (0.50), 0.30	-0.14 (0.18), 0.43	-0.02 (0.02), 0.31	0.27 (0.17), 0.11

^aAll brain measures are given as a percentage of total intracranial brain volume, except for the volume of white matter lesions, which were adjusted for the volume of white matter.

^bAdjusted for age, educational level, cardiovascular disease, hypertension and number of medications.

Supplementary Table 3. Linear regression model for the age-adjusted association between ESR polymorphisms and brain measures^a in women.

Model	N	Grey Matter	White Matter	Hippocampus	Corpus Callosum	White Matter Lesions
		Beta (SE), p-value	Beta (SE), p-value	Beta (SE), p	Beta (SE), p	Beta (SE), p-value
<u>ESR1</u>						
<i>rs2234693</i> : C allele	205	1	1	1	1	1
TT	90	-0.28 (0.33), 0.38	0.25 (0.24), 0.30	0.12 (0.08), 0.14	0.008 (0.01), 0.46	0.24 (0.10), 0.02*
<i>rs9340799</i> : G allele	171	1	1	1	1	1
AA	124	-0.13 (0.30), 0.66	0.29 (0.22), 0.20	0.12 (0.07), 0.11	0.00 (0.01), 0.98	0.11 (0.09), 0.23
<u>ESR2</u>						
<i>rs1271572</i> : T allele	206	1	1	1	1	1
GG	89	-0.16 (0.33), 0.64	-0.17 (0.24), 0.49	0.00 (0.08), 0.99	-0.003 (0.01), 0.81	-0.004 (0.10), 0.97
<i>rs4986938</i> : A allele	202	1	1	1	1	1
GG	93	0.47 (0.33), 0.15	0.09 (0.25), 0.70	0.12 (0.08), 0.12	0.01 (0.01), 0.31	-0.05 (0.10), 0.62
<i>rs1256049</i> : A allele	26	1	1	1	1	1
GG	269	-0.32 (0.54), 0.55	-0.12 (0.40), 0.76	-0.10 (0.13), 0.46	-0.02 (0.02), 0.32	-0.04 (0.17), 0.80

^aAll brain measures are given as a percentage of total intracranial brain volume, except for the volume of white matter lesions, which were adjusted for the volume of white matter. *p<0.05