The C677T Variant in *MTHFR* Modulates Associations Between Brain Integrity, Mood, and Cognitive Functioning in Old Age

Supplemental Information

Table S1. Total medial orbitofrontal volumes by genotype groups (N=640)

	CC	**CT**	**TT**	**Total**
N	273	275	92	640
Medial Orbitofrontal Volumes (in mm^3)	7,455.20 (± 1,027.22) [7,451.00]	7,514.64 (± 941.54) [7,475.00]	7,200.50 (± 973.04) [7,199.50]	7,444.13 (± 987.35) [7,435.50]
Standardized Volumes (z-scores)	0.01 (± 1.04) [0.01]	0.07 (± 0.95) [0.03]	-0.25 (± 0.99) [-0.25]	0.00 (± 1.00) [-.01]

N indicates sample sizes. Average volumes of the medial orbitofrontal cortices (in mm^3) and standardized volumes (z-scores) are followed by standard deviations in parentheses. Median volumes are indicated in brackets.

Table S2. Results of multiple regression analyses: Predictors of medial orbitofrontal volumes and plasma homocysteine

Dependent Variable	C677T	Diagnosis	Sex	Age	Corrected Model
mOFC Volumes (N=640)	0.033 (3.428) [2]	<0.001 (19.295) [2]	<0.001 (74.000) [1]	<0.001 (44.541) [1]	<0.001 (25.868) [6]
mOFC Volumes (Recessive Model)	0.009 (6.814) [1]	<0.001 (19.554) [2]	<0.001 (74.219) [1]	<0.001 (44.556) [1]	<0.001 (31.077) [5]
Homocysteine (N=732)	<0.001 (10.375) [2]	0.016 (4.153) [2]	<0.001 (24.991) [1]	<0.001 (28.839) [1]	<0.001 (14.857) [6]
Homocysteine (Recessive Model)	<0.001 (20.114) [1]	0.018 (4.053) [2]	<0.001 (25.342) [1]	<0.001 (28.893) [1]	<0.001 (17.708) [5]

Each row illustrates results of a separate GLM using the following equation: Dependent variable = C677T genotype + diagnosis + sex + age + intercept + error. The dependent variable and sample size are identified in the first column. For completeness, results obtained using a recessive model of minor T allele effects are presented below the default (additive) results discussed in the manuscript. *p*-values are followed by *F*-ratios in parentheses and degrees of freedom in brackets.

Table S3. Results of multiple regression analyses: Predictors of plasma homocysteine in the whole sample and by Vitamin B_{12} deficiency status

Dependent Variable	C677T	Diagnosis	Sex	Age	Vitamin B_{12} Deficiency	C677T * Vitamin B_{12}	Corrected Model
Homocysteine (N=675)	<0.001 (12.143) [2]	0.062 (2.787) [2]	<0.001 (23.030) [1]	<0.001 (27.032) [1]	0.021 (5.348) [1]	0.011 (4.529) [2]	<0.001 (10.007) [9]
Homocysteine (Recessive Model)	<0.001 (21.469) [1]	0.079 (2.553) [2]	<0.001 (23.898) [1]	<0.001 (27.225) [1]	0.005 (7.987) [1]	0.007 (7.320) [1]	<0.001 (12.450) [7]
Homocysteine (B_{12} Deficient N=83)	0.008 (5.122) [2]	0.572 (0.563) [2]	0.541 (0.377) [1]	0.023 (5.366) [1]			0.006 (3.270) [6]
Homocysteine (B_{12} Deficient Recessive)	0.003 (9.101) [1]	0.503 (0.694) [2]	0.462 (0.547) [1]	0.022 (5.498) [1]			0.005 (3.692) [5]
Homocysteine (Non-Deficient N=592)	0.055 (2.911) [2]	0.010 (4.684) [2]	<0.001 (24.127) [1]	<0.001 (21.467) [1]			<0.001 (10.925) [6]
Homocysteine (Non-Deficient Recessive)	0.019 (5.513) [1]	0.010 (4.656) [2]	<0.001 (24.261) [1]	<0.001 (21.654) [1]			<0.001 (13.062) [5]

Rows 1-2 illustrate results of a GLM using the following equation: Plasma homocysteine = C677T genotype + diagnosis + sex + age + vitamin B_{12} deficiency status + vitamin B_{12} deficiency*genotype + intercept + error. Row 3-4 illustrate results in deficient individuals. Rows 5-6 present results in non-deficient subjects. For completeness, results obtained using a recessive model of minor T allele effects are presented below the default (additive) results discussed in the manuscript. *p*-values are followed by *F*-ratios in parentheses and degrees of freedom in brackets.

Table S4. Results of multiple regression analyses: Predictors of mood

Dependent Variable: GDS-15		Homo-cysteine	Vitamin B_{12} Deficiency	MMSE	mOFC Volumes	Age	Sex	Corrected Model
GDS-15 (N=587)	0.256 (1.368) [2]	0.823 (0.050) [1]	0.961 (0.002) [1]	<0.001 (12.808) [1]	0.005 (7.840) [1]	0.107 (2.609) [1]	0.527 (0.401) [1]	<0.001 (3.855) [8]
GDS-15 (Recessive)	0.517 (0.421) [1]	0.860 (0.031) [1]	0.925 (0.009) [1]	<0.001 (13.285) [1]	0.005 (8.035) [1]	0.094 (2.6814) [1]	0.533 (0.388) [1]	<0.001 (4.066) [7]

This table illustrates results of a GLM using the following equation: GDS-15 = C677T genotype + plasma homocysteine + vitamin B_{12} deficiency status + MMSE + mOFC volumes + age + sex + intercept + error. For completeness, results obtained using a recessive model of minor T allele effects are presented below the default (additive) results discussed in the manuscript. *p*-values are followed by *F*-ratios in parentheses and degrees of freedom in brackets.

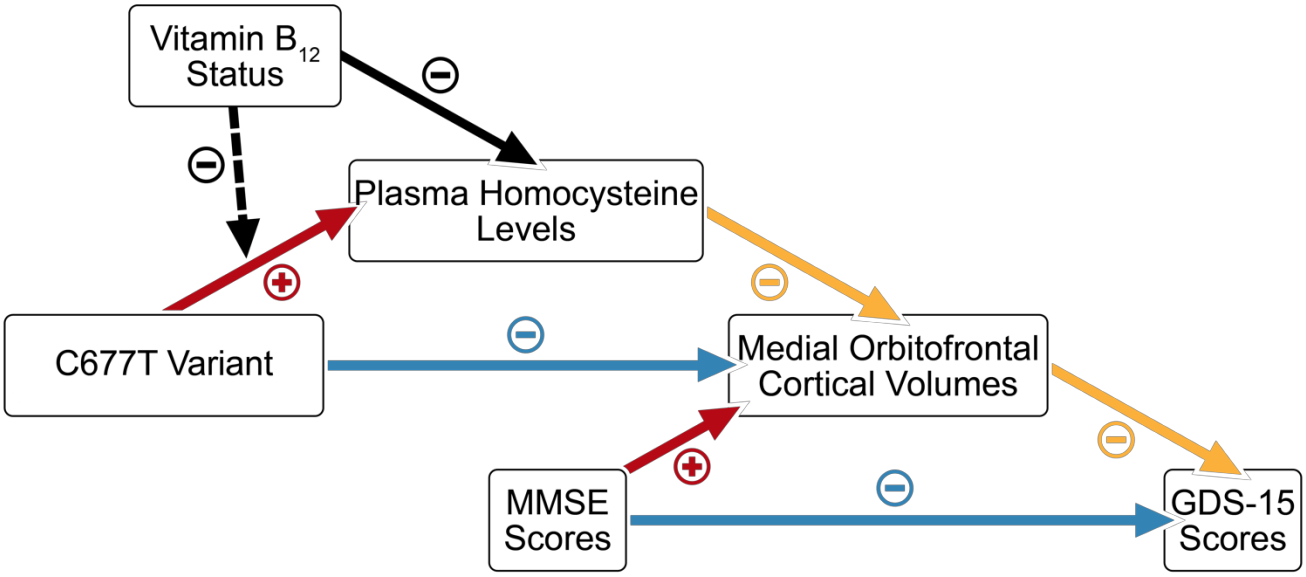

Figure S1. Summary of proposed model. Black arrows illustrate a simple association between two variables; dotted arrows denote moderation; colored arrows indicate mediation. A moderator variable influences the strength of a relationship between two other variables, while a mediator variable explains this relationship. Increased plasma homocysteine mediates the association between *MTHFR* genotype and lower medial orbitofrontal volumes, and these volumes mediate the association between MMSE and GDS-15 scores. Vitamin B_{12} deficiency moderates the association between the C677T variant and increased homocysteine; it is also an independent predictor of elevated homocysteine.