Supplementary Materials

Modeling cholesterol metabolism by gene expression profiling in the hippocampus

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Table S1

Cholesterol metabolite index. Fifty one cholesterol metabolites were included in the brain cholesterol metabolism model, plus acetate (M1) and coenzyme A (M2). The index (M) is used to ease location of metabolites mentioned in the text.

M1	acetate	M28	4alpha-carboxy-5alpha-cholesta-8-en-3beta-ol
M2	coenzyme A	M29	5alpha-cholesta-8-en-3-one
M3	acetyl-CoA	M30	zymostenol
M4	acetoacetyl-CoA	M31	7-dehydrodesmosterol
M5	3-hydroxy-3-methyl-glutaryl CoA	M32	desmosterol
M6	mevalonate	M33	4,4-dimethyl-14alpha-hydroxymethyl-5alpha-cholesta-8,24-dien-3beta-ol
M7	mevalonate-5 phosphate	M34	4,4-dimethyl-14alpha-formyl-5alpha-cholesta-8,24-dien-3beta-ol
M8	mevalonate-5-pyrophosphate	M35	4,4-dimethyl-5alpha-cholesta-8,14,24-trien-3beta-ol
M9	delta3-isopentenyl pyrophosphate	M36	4,4-dimethyl-5alpha-cholesta-8,24-dien-3beta-ol
M10	dimethylallyl pyrophosphate	M37	4alpha-hydroxymethyl-4beta-methyl-5alpha-cholesta-8,24-dien-3beta-ol
M11	geranyl pyrophosphate	M38	4alpha-formyl-4beta-methyl-5alpha-cholesta-8,24-dien-3beta-ol
M12	farnesyl pyrophosphate	M39	4alpha-carboxy-4beta-methyl-5alpha-cholesta-8,24-dien-3beta-ol
M13	squalene	M40	4alpha-methyl-5alpha-cholesta-8,24-dien-3-one
M14	(S)-squalene-2,3-epoxide	M41	4alpha-methyl-zymosterol
M15	lanosterol	M42	4alpha-hydroxymethyl-5alpha-cholesta-8,24-dien-3beta-ol
M16	24,25-dihydrolanosterol	M43	4alpha-formyl-5alpha-cholesta-8,24-dien-3beta-ol
M17	4,4-dimethyl-14alpha-hydroxymethyl-5alpha-cholesta-8-en-3beta-ol	M44	4alpha-carboxy-5alpha-cholesta-8,24-dien-3beta-ol
M18	4,4-dimethyl-14alpha-formyl-5alpha-cholesta-8-en-3beta-ol	M45	5alpha-cholesta-8,24-dien-3-one
M19	4,4-dimethyl-5alpha-cholesta-8,14-dien-3beta-ol	M46	zymosterol
M20	4,4-dimethyl-5alpha-cholesta-8-en-3beta-ol	M47	5alpha-cholesta-7,24-dien-3beta-ol
M21	4alpha-hydroxymethyl-4beta-methyl-5alpha-cholesta-8-en-3beta-ol	M48	lathosterol

M22	4alpha-formyl-4beta-methyl-5alpha-cholesta-8-en-3beta-ol	M49	7-dehydro-cholesterol
M23	4alpha-carboxy-4beta-methyl-5alpha-cholesta-8-en-3beta-ol	M50	cholesterol
M24	4alpha-methyl-5alpha-cholesta-8-en-3-one	M51	24-hydroxy-cholesterol
M25	4alpha-methyl-cholesta-8-enol	M52	27-hydroxy-7-dehydrocholesterol
M26	4alpha-hydroxymethyl-5alpha-cholesta-8-en-3beta-ol		
M27	4alpha-formyl-5alpha-cholesta-8-en-3beta-ol		

Table S2

RN: Reaction name; R: rate constant (k_f, forward; k_b, backward); Base: Baseline values; HD: Huntington's disease; IAD, MAD, SAD: incipient, moderate, and severe Alzheimer's disease.

RN	Enzyme	Reaction	R	Base	HD	IAD	MAD	SAD
Mevalonate-Lanosterol								
ML1	AACS	acetate + coenzyme A → acetyl-CoA	k_f	0.557	0.601	0.566	0.566	0.566
ML2	ACAT1	2 * acetyl-CoA ↔acetoacetyl-CoA + coenzyme A	k_f	0.798	0.849	0.558	0.558	0.558
			k_b	0.798	0.849	0.558	0.558	0.558
ML3	HMGCS1	acetyl-CoA + acetoacetyl-CoA + H2O → 3-hydroxy-3-methyl-glutaryl CoA + coenzyme A	k_f	1.000	0.994	0.698	0.698	0.698
ML4	HMGCR	3-hydroxy-3-methyl-glutaryl CoA + 2 * NADPH + H+ → mevalonate + 2 * $NADP^+$ + coenzyme A	k_f	0.233	0.178	0.233	0.233	0.233
ML5	MVK	mevalonate + ATP + Mg^{++} → mevalonate-5 phosphate + ADP	k_f	0.283	0.283	0.326	0.320	0.407
ML6	PMVK	mevalonate-5 phosphate + ATP + Mg^{++} → mevalonate-5-pyrophosphate + ADP	k_f	0.631	0.707	0.631	0.631	0.631
ML7	MVD	mevalonate-5-pyrophosphate + ATP → delta3-isopentenyl pyrophosphate + ADP + Pi + CO_2	k_f	0.286	0.274	0.286	0.286	0.286
ML8	IDI2	delta3-isopentenyl pyrophosphate + Mg^{++} ↔ dimethylallyl pyrophosphate	k_f	0.061	0.057	0.061	0.061	0.061
			k_b	0.061	0.057	0.061	0.061	0.061
ML9	DMTT (FDPS)	delta3-isopentenyl pyrophosphate + dimethylallyl pyrophosphate + PPi → geranyl pyrophosphate	k_f	0.765	0.845	0.759	0.963	0.999
ML10	GTT (FDPS)	delta3-isopentenyl pyrophosphate + geranyl pyrophosphate → farnesyl pyrophosphate + PPi	k_f	0.765	0.845	0.759	0.963	0.999
ML11	FDFT1	2 * farnesyl pyrophosphate +	k_f	0.093	0.124	0.083	0.112	0.122

		NADPH + H^+ → squalene + $NADP^+$						
ML12	SQLE	squalene + O_2 + NADPH + H^+ → (S)-squalene-2,3-epoxide + H_2O	k_f	1.000	1.000	1.000	1.000	1.000
ML13	LSS	(S)-squalene-2,3-epoxide → lanosterol	k_f	0.014	0.014	0.011	0.018	0.020
Cholesterol I								
ChI1	CYP51A1	lanosterol + NADPH + O_2 → 4,4-dimethyl-14alpha-hydroxymethyl-5alpha-cholesta-8,24-dien-3beta-ol + $NADP^+$ + H_2O	k_f	0.408	0.410	0.409	0.409	0.409
ChI2	CYP51A2	4,4-dimethyl-14alpha-hydroxymethyl-5alpha-cholesta-8,24-dien-3beta-ol + NADPH + O_2 → 4,4-dimethyl-14alpha-formyl-5alpha-cholesta-8,24-dien-3beta-ol + $NADP^+$ + 2 * H_2O	k_f	0.408	0.410	0.409	0.409	0.409
ChI3	CYP51A3	4,4-dimethyl-14alpha-formyl-5alpha-cholesta-8,24-dien-3beta-ol + NADPH + O2 → 4,4-dimethyl-5alpha-cholesta-8,14,24-trien-3beta-ol + $NADP^+$ + H_2O + formate	k_f	0.408	0.410	0.409	0.409	0.409
ChI4	LBR	4,4-dimethyl-5alpha-cholesta-8,14,24-trien-3beta-ol + NADPH →4,4-dimethyl-5alpha-cholesta-8,24-dien-3beta-ol + $NADP^+$	k_f	0.002	0.002	0.002	0.002	0.002
ChI5	DHCR14	4,4-dimethyl-5alpha-cholesta-8,14,24-trien-3beta-ol + NADPH → 4,4-dimethyl-5alpha-cholesta-8,24-dien-3beta-ol + $NADP^+$	k_f	0.005	0.005	0.005	0.005	0.005
ChI6	SC4MOL	4,4-dimethyl-5alpha-cholesta-8,24-dien-3beta-ol + NADPH + O2 → 4alpha-hydroxymethyl-4beta-methyl-5alpha-cholesta-8,24-dien-3beta-ol + $NADP^+$ + H_2O	k_f	0.455	0.471	0.455	0.455	0.455
ChI6	SC4MOL	4alpha-hydroxymethyl-4beta-methyl-5alpha-cholesta-8,24-dien-3beta-ol + NADPH + O_2 → 4alpha-formyl-4beta-methyl-5alpha-cholesta-8,24-dien-3beta-ol + $NADP^+$ + 2 * H_2O	k_f	0.455	0.471	0.455	0.455	0.455
ChI7	SC4MOL	4alpha-formyl-4beta-methyl-5alpha-cholesta-8,24-dien-3beta-ol + NADPH + O_2 → 4alpha-carboxy-4beta-methyl-5alpha-cholesta-8,24-dien-3beta-ol + $NADP^+$ + H_2O	k_f	0.455	0.471	0.455	0.455	0.455

ChI8	NSDHL	4alpha-carboxy-4beta-methyl-5alpha-cholesta-8,24-dien-3beta-ol + $NADP^+$ → 4alpha-methyl-5alpha-cholesta-8,24-dien-3-one + NADPH + CO_2	k_f	0.568	0.568	0.665	0.696	0.784
ChI9	HSD17B7	4alpha-methyl-5alpha-cholesta-8,24-dien-3-one + NADPH →4alpha-methyl-zymosterol + NADP+	k_f	0.137	0.172	0.194	0.236	0.259
ChI10	SC4MOL	4alpha-methyl-zymosterol + NADPH + O_2 →4alpha-hydroxymethyl-5alpha-cholesta-8,24-dien-3beta-ol + $NADP^+$ + H_2O	k_f	0.455	0.471	0.455	0.455	0.455
ChI11	SC4MOL	4alpha-hydroxymethyl-5alpha-cholesta-8,24-dien-3beta-ol + NADPH + O_2 →4alpha-formyl-5alpha-cholesta-8,24-dien-3beta-ol + $NADP^+$ + 2 * H_2O	k_f	0.455	0.471	0.455	0.455	0.455
ChI12	SC4MOL	4alpha-formyl-5alpha-cholesta-8,24-dien-3beta-ol + NADPH + O_2 →4alpha-carboxy-5alpha-cholesta-8,24-dien-3beta-ol + $NADP^+$ + H_2O	k_f	0.455	0.471	0.455	0.455	0.455
ChI13	NSDHL	4alpha-carboxy-5alpha-cholesta-8,24-dien-3beta-ol + $NADP^+$ →5alpha-cholesta-8,24-dien-3-one + NADPH + CO_2	k_f	0.568	0.568	0.665	0.696	0.784
ChI14	HSD17B7	5alpha-cholesta-8,24-dien-3-one + NADPH →zymosterol + $NADP^+$	k_f	0.137	0.172	0.194	0.236	0.259
ChI15	EBPL	zymosterol →5alpha-cholesta-7,24-dien-3beta-ol	k_f	0.835	0.887	0.898	0.855	0.649
ChI16	DHCR24	5alpha-cholesta-7,24-dien-3beta-ol + NADPH → lathosterol + $NADP^+$	k_f	0.325	0.307	0.326	0.326	0.326
ChI17	SCD5L	lathosterol + O_2 + NADPH →7-dehydro-cholesterol + H2O + $NADP^+$	k_f	0.195	0.183	0.186	0.163	0.167
ChI18	DHCR7	7-dehydro-cholesterol + NADPH → cholesterol + $NADP^+$	k_f	0.614	0.718	0.657	0.514	0.466
	Cholesterol II							
ChII1	DHCR24	lanosterol + NADPH → 24,25-dihydrolanosterol + $NADP^+$	k_f	0.325	0.307	0.326	0.326	0.326
ChII2	CYP51	24,25-dihydrolanosterol + NADPH + O_2 →4,4-dimethyl-14alpha-hydroxymethyl-5alpha-cholesta-8-en-3beta-ol + $NADP^+$ + H_2O	k_f	0.408	0.410	0.409	0.409	0.409
ChII3	CYP51	4,4-dimethyl-14alpha-hydroxymethyl-5alpha-cholesta-8-en-3beta-ol + NADPH + O_2 →4,4-dimethyl-	k_f	0.408	0.410	0.409	0.409	0.409

		14alpha-formyl-5alpha-cholesta-8-en-3beta-ol + $NADP^+$ + 2 * H_2O						
ChII4	CYP51	4,4-dimethyl-14alpha-formyl-5alpha-cholesta-8-en-3beta-ol + NADPH + O_2 →4,4-dimethyl-5alpha-cholesta-8,14-dien-3beta-ol + $NADP^+$ + H_2O + formate	k_f	0.408	0.410	0.409	0.409	0.409
ChII5	LBR	4,4-dimethyl-5alpha-cholesta-8,14-dien-3beta-ol + NADPH →4,4-dimethyl-5alpha-cholesta-8-en-3beta-ol + $NADP^+$	k_f	0.002	0.002	0.002	0.002	0.002
ChII6	DHCR14	4,4-dimethyl-5alpha-cholesta-8,14-dien-3beta-ol + NADPH → 4,4-dimethyl-5alpha-cholesta-8-en-3beta-ol + $NADP^+$	k_f	0.005	0.004	0.005	0.005	0.005
ChII7	SC4MOL	4,4-dimethyl-5alpha-cholesta-8-en-3beta-ol + NADPH + O_2 →4alpha-hydroxymethyl-4beta-methyl-5alpha-cholesta-8-en-3beta-ol + $NADP^+$ + H_2O	k_f	0.455	0.470	0.455	0.455	0.455
ChII8	SC4MOL	4alpha-hydroxymethyl-4beta-methyl-5alpha-cholesta-8-en-3beta-ol + NADPH + O_2 →4alpha-formyl-4beta-methyl-5alpha-cholesta-8-en-3beta-ol + $NADP^+$ + 2 * H_2O	k_f	0.455	0.470	0.455	0.455	0.455
ChII9	SC4MOL	4alpha-formyl-4beta-methyl-5alpha-cholesta-8-en-3beta-ol + NADPH + O_2 →4alpha-carboxy-4beta-methyl-5alpha-cholesta-8-en-3beta-ol + $NADP^+$ + H_2O	k_f	0.455	0.470	0.455	0.455	0.455
ChII10	NSDHL-1	4alpha-carboxy-4beta-methyl-5alpha-cholesta-8-en-3beta-ol + $NADP^+$ →4alpha-methyl-5alpha-cholesta-8-en-3-one + CO_2 + NADPH	k_f	0.568	0.568	0.665	0.696	0.784
ChII11	HSD17B7	4alpha-methyl-5alpha-cholesta-8-en-3-one + NADPH →4alpha-methyl-cholesta-8-enol + $NADP^+$	k_f	0.137	0.171	0.194	0.236	0.259
ChII12	SC4MOL	4alpha-methyl-cholesta-8-enol + NADPH + O_2 →4alpha-hydroxymethyl-5alpha-cholesta-8-en-3beta-ol + $NADP^+$ + H_2O	k_f	0.455	0.470	0.455	0.455	0.455
ChII13	SC4MOL	4alpha-hydroxymethyl-5alpha-cholesta-8-en-3beta-ol + NADPH + O_2 →4alpha-formyl-5alpha-cholesta-8-en-3beta-ol + $NADP^+$ + 2 * H_2O	k_f	0.455	0.470	0.455	0.455	0.455

ChII14	SC4MOL	4alpha-formyl-5alpha-cholesta-8-en-3beta-ol + NADPH + O_2 → 4alpha-carboxy-5alpha-cholesta-8-en-3beta-ol + $NADP^+$ + H_2O	k_f	0.455	0.470	0.455	0.455	0.455
ChII15	NSDHL	4alpha-carboxy-5alpha-cholesta-8-en-3beta-ol + NADP+ →5alpha-cholesta-8-en-3-one + NADPH + CO_2	k_f	0.568	0.568	0.665	0.696	0.784
ChII16	HSD17B7	5alpha-cholesta-8-en-3-one + NADPH →zymostenol + $NADP^+$	k_f	0.137	0.171	0.194	0.236	0.259
ChII17	EBPL	zymostenol →lathosterol	k_f	0.835	0.887	0.898	0.855	0.649
Cholesterol III								
ChIII1	SC5DL	5alpha-cholesta-7,24-dien-3beta-ol + NADPH + O_2 →7-dehydrodesmosterol + $NADP^+$ + 2 * H_2O	k_f	0.195	0.183	0.186	0.163	0.167
ChIII2	DHCR7	7-dehydrodesmosterol + NADPH → desmosterol + $NADP^+$	k_f	0.614	0.717	0.657	0.514	0.466
ChIII3	DHCR24	desmosterol + NADPH → cholesterol + $NADP^+$	k_f	0.325	0.307	0.326	0.326	0.326
Degradation								
D1	CYP46A1	cholesterol → 24-hydroxy-cholesterol	k_f	1.000	0.526	1.000	1.000	1.000
D2	CYP27B1	7-dehydro-cholesterol → 27-hydroxy-7-dehydro-cholesterol	k_f	0.030	0.037	0.030	0.030	0.030

Table S3

	Enzymes	**Base**	**HD**	**IAD**	**MAD**	**SAD**
E1	AACS	0.557	0.601	0.566	0.566	0.566
E2	ACAT1	0.798	0.849	0.558	0.558	0.558
E3	HMGCS1	1.000	0.994	0.698	0.698	0.698
E4	HMGCR	0.233	0.178	0.233	0.233	0.233
E5	MVK	0.283	0.283	0.326	0.320	0.407
E6	PMVK	0.631	0.707	0.631	0.631	0.631
E7	MVD	0.286	0.274	0.286	0.286	0.286
E8	IDI2	0.061	0.057	0.061	0.061	0.061
E9	FDPS	0.765	0.845	0.759	0.963	0.999
E10	FDFT1	0.093	0.124	0.083	0.112	0.122
E11	SQLE	1.000	1.000	1.000	1.000	1.000
E12	LSS	0.014	0.014	0.011	0.018	0.020
E13	CYP51	0.408	0.410	0.409	0.409	0.409
E14	LBR	0.002	0.002	0.002	0.002	0.002
E15	DHCR14 (coded by Tm7sf2)	0.005	0.005	0.005	0.005	0.005
E16	DHCR24	0.325	0.307	0.325	0.325	0.325
E17	SC4MOL	0.455	0.471	0.455	0.455	0.455
E18	NSDHL	0.568	0.568	0.665	0.696	0.784
E19	HSD17B7	0.137	0.172	0.194	0.236	0.259
E20	EBPL	0.835	0.887	0.898	0.855	0.649
E21	SC5DL	0.195	0.183	0.186	0.163	0.167
E22	DHCR7	0.614	0.718	0.657	0.514	0.466
E23	CYP46A1	1.000	0.526	1.000	1.000	1.000
E24	CYP27B1	0.030	0.037	0.030	0.030	0.030

Table S4
Genes involved in cholesterol metabolism.

Gene abbreviation	Gene name
Aacs	Acetoacetyl-CoA synthease
Acat1	Acetyl-Coenzyme A acetyltransferase **1**
Hmgcs1	3-hyrdroxy-3-methylglutaryl-Coenzyme A synthase 1
Hmgcr	3-hydroxy 3-methylglutaryl-Coenzyme A reductase
Mvk	Mevalonate kinase
Pmvk	Phosphomevalonate Kinase
Mvd	Diphosphomevalonate decarboxylase
Idi2	Isopentenyl diphosphate isomerase 2
Fdps	Farnesyl diphosphate synthetase
Fdft1	Farnesyl diphosphate farnesyl transferase 1 (squalene synthase)
Sqle	Squalene epoxidase
Lss	Lanosterol synthase
Cyp51	Cytochrome P450, family 51
Tm7sf2 (produces DHCR14)	Transmembrane 7 superfamily member 2
Lbr	Lamin B receptor
Sc4mol	Sterol-C4-methyl oxidase-like
Hsd17b7	Hydroxysteroid (17-beta) dehydrogenase 7
Ebpl	Phenylalkylamine Ca2+ antagonist, emopamil binding protein
Dhcr24	24-dehydrocholesterol reductase
Sc5dl	Sterol-C5-desaturase
Dhcr7	7-dehydrocholesterol reductase
Cyp46a1	Cytochrome P450, family 46, subfamily a, polypeptide 1
Cyp39a1	Cytochrome P450, family 39, subfamily a, polypeptide 1
Cyp27b1	Cytochrome P450, family 27, subfamily b, polypeptide 1