Influence of *FKBP5* polymorphism and DNA methylation on structural changes of the brain in major depressive disorder

- Supplementary information -

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The methods for Sodium Bisulfite modification and Pyrosequencing.

Bisulfite modified gDNA was prepared using the EZ DNA Methylation-Lighting^{TM} kit (Zymo Research, USA) according to the manufacturer's instructions. The bisulfite reaction was carried out on 500 ng gDNA. The reaction volume was adjusted to 20 μL with sterile water and 130 μL of CT conversion Reagent was added. Sample tubes were placed in a thermal cycler (MJ Research) and the following steps were performed: 8 min at 98°C, 60 min at 54°C, and storage at 4°C for up to 20 h.

DNA was purified using the EZ DNA Methylation-Lighting^{TM} kit (Zymo Research, USA). The converted samples were added to a Zymo-Spin IC^{TM} Column containing 600 μL of the M-Binding Buffer and mixed by inverting the column several times. The column was centrifuged at full speed for 30 s and the flow-through was discarded. The column was washed by adding 200 μL of M-Wash Buffer and centrifuging at full speed. Then 200 μL of M-Desulphonation Buffer was added to the column, which was incubated at room temperature (20–30°C) for 15–20 min. After incubation, the column was centrifuged at full speed for 30 s. The column was washed twice by adding 200 μL of M-Wash Buffer and centrifuging at full speed. The converted gDNA was eluted by adding 20 μL of M-Elution Buffer to the column and centrifuging. DNA samples were finally stored at −20°C until further use.

The primers were designed using Pyrosequencing Assay Design Software v2.0 (Qiagen). The PCR reaction was carried out in a volume of 20 μL with 20 ng or more of converted gDNA, the PCR premixture (Enzynomics, Korea), 1 μL of 10 pmol/μL Primer-S, and 1 μL of 10 pmol/μL biotinylated-Primer-As. Amplification was carried out according to the general guidelines suggested for Pyrosequencing: denaturing at 95°C for 10 min, followed by 45 cycles of 95°C for 30 s, at 60°C for 30 s, at 72°C for 30 s and a final extension at 72°C for 5 min. The PCR reaction (2 μL) was confirmed by electrophoresis in a 2% Agarose gel and visualized by ethidium bromide staining. The ssDNA template was prepared from 16–18 μL biotinylated PCR product using streptavidin Sepharose® HP beads (Amersham Biosciences, Sweden) following the PSQ 96 sample preparation guide using multichannel pipettes. Fifteen picomoles of the respective sequencing primer were added for analysis. Sequencing was performed on a PyroMark ID system with the Pyro Gold reagent kit (Qiagen) according to the manufacturer's instructions, without further optimization.

Target CpG islands and the primers for pyrosequencing.

Gene	Primer		Size (bp)
FKBP5 Intron 7	Forward	5′-TGGGATAATAATTTGGAGTTATAGTGTA-3′	187
	Biotinylated-reverse	5′-ATTCCCTTATTTATTCCTAAACTTATTCTT-3′	
	Sequencing primer	5′-GGAGTTATAGTGTAGGTTTT-3′	

Table S1. Demographic and clinical characteristics of patients with major depressive disorder and healthy controls included in the methylation analysis.

	MDD (n=104)	**HC (n=82)**	p value
Age	43.76 ± 11.91	40.13 ± 14.30	0.067
Gender (female)	83	56	0.090
Education level			
Elementary and middle school	24	13	
High school or college/university	73	58	0.190
Above graduate school	7	11	
HDRS-17 score	14.68 ± 8.14	2.28 ± 2.14	<0.001
Duration of illness (months)	46.19 ± 48.48		
FKBP5 gene rs1360780			
CC	65	53	
CT	36	28	0.731
TT	3	1	
HWE	0.450	0.198	
CC	65	53	0.878
CT + TT	39	29	
Drug-naïve / Antidepressant	49 / 55		
CC	29 / 36		0.548
CT + TT	20 / 19		
Antidepressant type			
SSRI	28		
SNRI	9		
NDRI	5		
NaSSA	3		
Combination	10		

Data represent mean ± standard deviation for age, HDRS-17 scores, and duration of illness.

The p values for distributions of gender, education level, FKBP5 genotype, and drug-naïve patients according to the genotype were obtained by chi-square test.

The p values for comparisons of age and HDRS-17 scores were obtained by independent t-test.

Allele frequencies (C/T): MDD patients 0.80/0.20, HC subjects 0.82/0.18.

MDD, major depressive disorder; HC, healthy controls; HDRS-17, Hamilton Depression Rating Scale; HWE, Hardy-Weinberg equilibrium; SSRI, serotonin and norepinephrine reuptake inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor; NDRI, norepinephrine-dopamine reuptake inhibitor; NaSSA, noradrenergic and specific serotonergic antidepressant; Combination, combinations of two or more types of antidepressant.

Table S2. List of the 38 cortical gyri.

Frontomarginal gyrus (of Wernicke)
Inferior occipital gyrus
Paracentral lobule
Subcentral gyrus (central operculum)
Transverse frontopolar gyrus
Anterior part of the cingulate gyrus
Middle-anterior part of the cingulate gyrus
Middle-posterior part of the cingulate gyrus
Dorsal posterior cingulate gyrus
Ventral posterior cingulate gyrus (isthmus of the cingulate gyrus)
Cuneus
Opercular part of the inferior frontal gyrus (Pars opercularis)
Orbital part of the inferior frontal gyrus (Pars orbitalis)
Triangular part of the inferior frontal gyrus (Pars triangularis)
Middle frontal gyrus
Superior frontal gyrus
Long insular gyrus
Short insular gyrus
Middle occipital gyrus
Superior occipital gyrus
Lateral occipito-temporal gyrus
Lingual gyrus
Parahippocampal gyrus
Orbital gyrus
Angular gyrus
Supramarginal gyrus
Superior parietal lobule
Postcentral gyrus
Precentral gyrus
Precuneus
Straight gyrus
Subcallosal gyrus
Anterior transverse temporal gyrus (of Heschl)
Lateral aspect of the superior temporal gyrus
Planum polare of the superior temporal gyrus

Planum temporale or temporal plane of the superior temporal gyrus
Inferior temporal gyrus
Middle temporal gyrus

Figure S1. Cortical surfaces labeled using Destrieux atlas of a subject's right hemisphere.

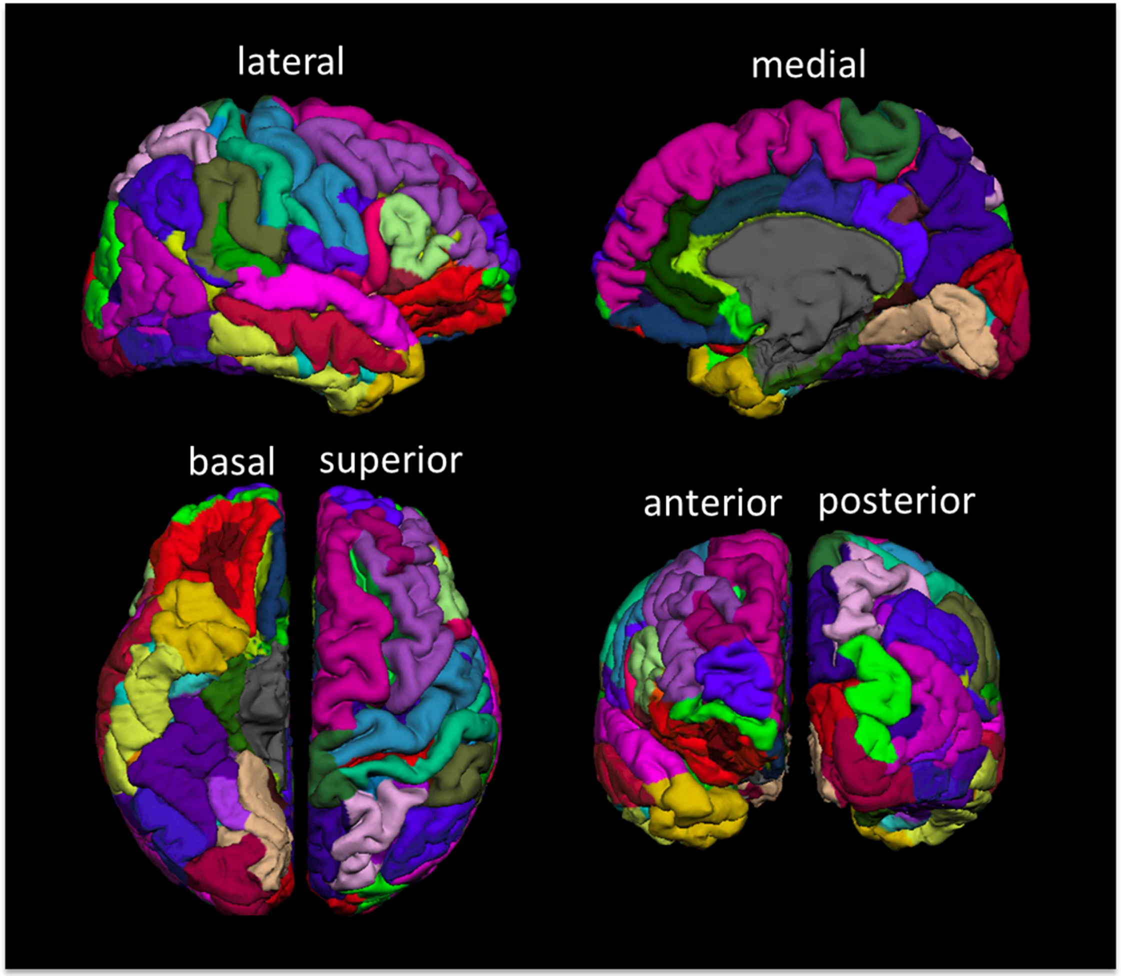

Table S3. Main-analysis investigating effect of diagnosis, genotype, and diagnosis-by-genotype interaction on cortical gray-matter volumes and thicknesses of whole-brain.

brain regions	**MDD vs. HC**			**CC vs. CT + TT**				**Diagnosis x Genotype interaction**		
	F	P_{uncorr}	P_{corr}	F	P_{uncorr}	P_{corr}		F	P_{uncorr}	P_{corr}
cortical volume										
L frontomarginal gyrus	0.166	0.684	0.989	4.701	0.031	0.265	CC > CT + TT	1.634	0.203	0.501
L inferior occipital gyrus	0.145	0.704	0.989	0.335	0.563	0.669		0.130	0.719	0.828
L paracentral lobule	3.049	0.082	0.782	0.429	0.513	0.639		0.018	0.892	0.968
L subcentral gyrus	0.368	0.545	0.989	5.986	0.015	0.206	CC > CT + TT	0.914	0.340	0.517
L transverse frontopolar gyrus	3.118	0.079	0.782	1.439	0.232	0.522		1.239	0.267	0.501
L anterior cingulate gyrus	0.96	0.328	0.989	2.324	0.129	0.409		2.850	0.093	0.393
L anterior midcingulate gyrus	0.304	0.582	0.989	0.724	0.396	0.605		0.422	0.517	0.689
L posterior midcingulate gyrus	0.944	0.333	0.989	0.745	0.389	0.605		3.454	0.065	0.289
L dorsal posterior cingulate gyrus	2.177	0.142	0.989	3.672	0.057	0.281		1.030	0.311	0.517
L ventral posterior cingulate gyrus	2.563	0.111	0.938	1.395	0.239	0.522		1.322	0.252	0.501
L cuneus	0.120	0.730	0.989	0.44	0.508	0.639		0.064	0.801	0.895
L pars opercularis	0.004	0.952	0.989	1.166	0.282	0.522		2.139	0.145	0.460
L pars orbitalis	0.002	0.965	0.989	0.402	0.527	0.645		1.607	0.206	0.501
L pars triangularis	1.387	0.240	0.989	1.223	0.270	0.522		11.074	0.001*	0.027*
L middle frontal gyrus	0.343	0.559	0.989	1.245	0.266	0.522		1.384	0.241	0.501
L superior frontal gyrus	0.026	0.873	0.989	3.593	0.060	0.281		0.002	0.967	0.979

L long insular gyrus	0.300	0.584	0.989		5.541	0.020	0.213	CC > CT + TT	0.003	0.956	0.979
L short insular gyrus	1.067	0.303	0.989		0.577	0.448	0.619		4.897	0.028	0.152
L middle occipital gyrus	3.063	0.082	0.782		0.159	0.690	0.760		5.545	0.020	0.124
L superior occipital gyrus	<0.001	0.983	0.989		0.627	0.429	0.615		0.452	0.502	0.689
L lateral occipito-temporal gyrus	0.087	0.769	0.989		0.607	0.437	0.615		0.174	0.677	0.816
L lingual gyrus	0.065	0.799	0.989		0.527	0.469	0.627		1.347	0.247	0.501
L parahippocampal gyrus	0.828	0.364	0.989		0.523	0.471	0.627		0.226	0.635	0.804
L orbital gyrus	0.65	0.421	0.989		2.846	0.093	0.351		1.028	0.312	0.517
L angular gyrus	3.304	0.071	0.782		0.036	0.850	0.907		0.634	0.427	0.624
L supramarginal gyrus	0.059	0.809	0.989		2.391	0.124	0.409		11.832	0.001*	0.027*
L superior parietal lobule	0.896	0.345	0.989		2.704	0.102	0.351		14.179	<0.001*	0.017*
L postcentral gyrus	0.001	0.971	0.989		5.087	0.025	0.240	CC > CT + TT	0.002	0.962	0.979
L precentral gyrus	0.008	0.927	0.989		0.003	0.960	0.960		0.517	0.473	0.678
L precuneus	0.320	0.572	0.989		1.174	0.280	0.522		6.337	0.013	0.114
L straight gyrus	0.580	0.447	0.989		0.219	0.641	0.727		1.258	0.263	0.501
L subcallosal gyrus	5.134	0.025	0.782	MDD > HC	1.519	0.219	0.522		0.004	0.951	0.979
L anterior transverse temporal gyrus	<0.001	0.989	0.989		5.879	0.016	0.206	CC > CT + TT	1.706	0.193	0.501
L lateral superior temporal gyrus	0.001	0.970	0.989		3.289	0.071	0.301		0.944	0.333	0.517
L planum polare	0.241	0.624	0.989		1.182	0.278	0.522		1.401	0.238	0.501
L planum temporale	0.600	0.440	0.989		0.717	0.398	0.605		0.949	0.331	0.517
L inferior temporal gyrus	0.982	0.323	0.989		0.797	0.373	0.605		1.750	0.187	0.501
L middle temporal gyrus	0.153	0.696	0.989		1.038	0.310	0.547		1.558	0.213	0.501
R frontomarginal gyrus	1.337	0.249	0.989		0.935	0.335	0.565		9.508	0.002*	0.043*
R inferior occipital gyrus	0.225	0.636	0.989		0.448	0.504	0.639		0.254	0.615	0.792

R paracentral lobule	1.692	0.195	0.989	0.029	0.865	0.907		1.177	0.279	0.501
R subcentral gyrus	0.367	0.546	0.989	19.996	<0.001*	0.001*	CC > CT + TT	1.395	0.239	0.501
R transverse frontopolar gyrus	0.053	0.818	0.989	0.631	0.428	0.615		5.111	0.025	0.146
R anterior cingulate gyrus	0.010	0.922	0.989	1.757	0.187	0.522		1.157	0.283	0.501
R anterior midcingulate gyrus	0.564	0.454	0.989	3.647	0.058	0.281		0.002	0.963	0.979
R posterior midcingulate gyrus	0.089	0.765	0.989	0.027	0.871	0.907		9.158	0.003*	0.043*
R dorsal posterior cingulate gyrus	0.551	0.459	0.989	0.317	0.574	0.671		6.213	0.014	0.114
R ventral posterior cingulate gyrus	0.043	0.835	0.989	1.123	0.290	0.526		0.915	0.340	0.517
R cuneus	0.126	0.723	0.989	1.249	0.265	0.522		0.373	0.542	0.710
R pars opercularis	0.206	0.651	0.989	5.956	0.016	0.206	CC > CT + TT	0.153	0.696	0.816
R pars orbitalis	0.016	0.898	0.989	0.788	0.376	0.605		2.013	0.158	0.479
R pars triangularis	0.006	0.941	0.989	1.891	0.171	0.519		0.151	0.698	0.816
R middle frontal gyrus	2.056	0.153	0.989	1.323	0.251	0.522		2.449	0.119	0.442
R superior frontal gyrus	0.615	0.434	0.989	3.194	0.075	0.302		0.080	0.777	0.882
R long insular gyrus	0.116	0.734	0.989	1.386	0.241	0.522		1.223	0.270	0.501
R short insular gyrus	0.045	0.831	0.989	0.190	0.663	0.741		2.402	0.123	0.442
R middle occipital gyrus	0.255	0.614	0.989	2.742	0.099	0.351		6.234	0.013	0.114
R superior occipital gyrus	0.184	0.668	0.989	0.636	0.426	0.615		1.251	0.265	0.501
R lateral occipito-temporal gyrus	0.138	0.710	0.989	0.064	0.801	0.870		0.459	0.499	0.689
R lingual gyrus	0.229	0.633	0.989	3.618	0.059	0.281		0.205	0.651	0.811
R parahippocampal gyrus	1.869	0.173	0.989	0.293	0.589	0.678		0.026	0.873	0.961
R orbital gyrus	0.001	0.976	0.989	3.530	0.062	0.281		5.762	0.017	0.120
R angular gyrus	1.466	0.227	0.989	0.005	0.944	0.957		0.441	0.508	0.689
R supramarginal gyrus	3.496	0.063	0.782	1.384	0.241	0.522		0.988	0.321	0.517

R superior parietal lobule	1.125	0.290	0.989		3.661	0.057	0.281		4.09	0.045	0.226
R postcentral gyrus	1.742	0.189	0.989		0.345	0.558	0.669		2.338	0.128	0.442
R precentral gyrus	0.035	0.852	0.989		3.577	0.060	0.281		0.875	0.351	0.523
R precuneus	0.283	0.595	0.989		1.559	0.213	0.522		5.942	0.016	0.119
R straight gyrus	9.341	0.003	0.194	MDD < HC	0.008	0.928	0.953		7.235	0.008	0.099
R subcallosal gyrus	0.431	0.512	0.989		0.505	0.478	0.627		<0.001	0.986	0.986
R anterior transverse temporal gyrus	1.690	0.195	0.989		8.331	0.004	0.110	CC > CT + TT	2.441	0.120	0.442
R lateral superior temporal gyrus	0.815	0.368	0.989		9.620	0.002	0.084	CC > CT + TT	1.213	0.272	0.501
R planum polare	0.062	0.804	0.989		1.270	0.261	0.522		1.448	0.230	0.501
R planum temporale	3.540	0.061	0.782		1.689	0.195	0.522		3.830	0.052	0.246
R inferior temporal gyrus	0.909	0.342	0.989		3.503	0.063	0.281		2.228	0.137	0.453
R middle temporal gyrus	<0.001	0.983	0.989		0.979	0.324	0.559		0.165	0.685	0.816
cortical thickness											
L frontomarginal gyrus	4.017	0.046	0.359	MDD < HC	3.745	0.054	0.425		0.002	0.963	0.984
L inferior occipital gyrus	0.918	0.339	0.584		0.084	0.772	0.939		2.191	0.140	0.898
L paracentral lobule	0.009	0.926	0.985		0.122	0.727	0.937		0.160	0.689	0.935
L subcentral gyrus	0.952	0.330	0.584		3.615	0.059	0.425		0.214	0.644	0.906
L transverse frontopolar gyrus	3.378	0.068	0.362		1.780	0.184	0.607		0.500	0.480	0.898
L anterior cingulate gyrus	3.077	0.081	0.362		2.404	0.123	0.518		0.111	0.739	0.943
L anterior mid-cingulate gyrus	0.176	0.676	0.812		0.095	0.759	0.939		0.243	0.622	0.906
L mid-posterior cingulate gyrus	0.483	0.488	0.686		1.495	0.223	0.652		1.094	0.297	0.898
L dorsal posterior cingulate gyrus	0.336	0.563	0.725		0.063	0.802	0.939		9.233	0.003	0.206
L ventral posterior cingulate gyrus	0.666	0.415	0.631		0.016	0.898	0.950		0.014	0.906	0.956
L cuneus	0.308	0.580	0.734		0.001	0.979	0.979		0.220	0.640	0.906

L pars opercularis	2.759	0.098	0.374		0.826	0.365	0.749		0.027	0.869	0.943
L pars orbitalis	1.205	0.274	0.565		0.369	0.544	0.817		3.163	0.077	0.898
L pars triangularis	1.162	0.282	0.565		2.635	0.106	0.504		1.130	0.289	0.898
L middle frontal gyrus	2.174	0.142	0.469		0.914	0.340	0.718		0.083	0.774	0.943
L superior frontal gyrus	1.637	0.202	0.518		0.472	0.493	0.797		0.052	0.820	0.943
L long insular gyrus	0.109	0.742	0.826		2.003	0.159	0.574		0.777	0.379	0.898
L short insular gyrus	0.154	0.695	0.812		5.349	0.022	0.359	CC > CT + TT	0.396	0.530	0.898
L middle occipital gyrus	1.598	0.208	0.518		2.671	0.104	0.504		0.737	0.392	0.898
L superior occipital gyrus	2.909	0.090	0.362		0.26	0.611	0.871		1.934	0.166	0.898
L lateral occipito-temporal gyrus	0.180	0.672	0.812		1.647	0.201	0.611		0.767	0.382	0.898
L lingual gyrus	0.375	0.541	0.725		0.057	0.812	0.939		1.782	0.183	0.898
L parahippocampal gyrus	0.572	0.450	0.655		0.05	0.823	0.939		1.222	0.270	0.898
L orbital gyrus	4.127	0.044	0.359	MDD < HC	0.957	0.329	0.718		0.077	0.782	0.943
L angular gyrus	1.579	0.210	0.518		0.925	0.337	0.718		0.475	0.492	0.898
L supramarginal gyrus	1.43	0.233	0.537		1.17	0.281	0.673		1.323	0.251	0.898
L superior parietal lobule	0.126	0.723	0.826		0.933	0.335	0.718		3.625	0.058	0.898
L postcentral gyrus	<0.001	0.990	1.000		0.752	0.387	0.751		0.032	0.859	0.943
L precentral gyrus	0.159	0.691	0.812		0.013	0.909	0.950		1.362	0.245	0.898
L precuneus	0.727	0.395	0.613		0.009	0.925	0.950		1.392	0.240	0.898
L straight gyrus	2.287	0.132	0.456		0.074	0.786	0.939		<0.001	0.984	0.984
L subcallosal gyrus	0.052	0.820	0.890		1.177	0.279	0.673		1.535	0.217	0.898
L anterior transverse temporal gyrus	<0.001	1.000	1.000		4.347	0.038	0.425	CC > CT + TT	0.372	0.543	0.898
L lateral superior temporal gyrus	0.893	0.346	0.584		3.539	0.061	0.425		0.066	0.797	0.943
L planum polare	4.531	0.035	0.359	MDD < HC	2.071	0.152	0.574		0.863	0.354	0.898

L planum temporale	1.108	0.294	0.573		0.184	0.668	0.907		0.521	0.471	0.898
L inferior temporal gyrus	0.556	0.457	0.655		2.97	0.086	0.504		0.473	0.492	0.898
L middle temporal gyrus	2.975	0.086	0.362		2.449	0.119	0.518		0.058	0.809	0.943
R frontomarginal gyrus	5.026	0.026	0.331	MDD < HC	1.718	0.192	0.607		0.351	0.554	0.898
R inferior occipital gyrus	1.969	0.162	0.514		0.106	0.745	0.939		0.577	0.448	0.898
R paracentral lobule	0.102	0.750	0.826		0.024	0.876	0.950		0.399	0.528	0.898
R subcentral gyrus	0.770	0.381	0.604		9.272	0.003	0.202	CC > CT + TT	0.452	0.502	0.898
R transverse frontopolar gyrus	6.341	0.013	0.331	MDD < HC	1.416	0.236	0.653		0.231	0.631	0.906
R anterior cingulate gyrus	11.909	0.001	0.052	MDD < HC	0.639	0.425	0.751		0.033	0.856	0.943
R anterior mid-cingulate gyrus	3.232	0.074	0.362		0.44	0.508	0.804		0.637	0.426	0.898
R mid-posterior cingulate gyrus	0.855	0.356	0.588		0.15	0.699	0.915		1.547	0.215	0.898
R dorsal posterior cingulate gyrus	0.002	0.960	0.997		0.002	0.966	0.979		4.719	0.031	0.898
R ventral posterior cingulate gyrus	5.286	0.023	0.331	MDD < HC	0.039	0.843	0.939		1.549	0.215	0.898
R cuneus	0.769	0.382	0.604		0.362	0.548	0.817		<0.001	0.984	0.984
R pars opercularis	5.459	0.020	0.331	MDD < HC	6.575	0.011	0.281	CC > CT + TT	0.473	0.492	0.898
R pars orbitalis	0.001	0.971	0.997		2.681	0.103	0.504		0.696	0.405	0.898
R pars triangularis	3.525	0.062	0.362		1.793	0.182	0.607		0.257	0.613	0.906
R middle frontal gyrus	2.585	0.110	0.396		0.715	0.399	0.751		0.434	0.511	0.898
R superior frontal gyrus	3.757	0.054	0.362		0.649	0.422	0.751		2.241	0.136	0.898
R long insular gyrus	2.895	0.090	0.362		0.734	0.393	0.751		0.543	0.462	0.898
R short insular gyrus	1.370	0.243	0.544		3.635	0.058	0.425		0.24	0.625	0.906
R middle occipital gyrus	0.955	0.330	0.584		0.562	0.454	0.763		0.758	0.385	0.898
R superior occipital gyrus	0.359	0.550	0.725		1.336	0.249	0.653		0.051	0.822	0.943
R lateral occipito-temporal gyrus	0.998	0.319	0.584		0.544	0.462	0.763		0.100	0.752	0.943

R lingual gyrus	0.36	0.549	0.725		0.595	0.441	0.762		0.349	0.555	0.898
R parahippocampal gyrus	1.184	0.278	0.565		3.734	0.055	0.425		1.127	0.290	0.898
R orbital gyrus	1.530	0.218	0.518		0.373	0.542	0.817		0.947	0.332	0.898
R angular gyrus	0.994	0.320	0.584		0.035	0.852	0.939		0.117	0.733	0.943
R supramarginal gyrus	3.989	0.047	0.359	MDD < HC	2.297	0.131	0.525		0.225	0.636	0.906
R superior parietal lobule	0.351	0.555	0.725		0.010	0.922	0.950		0.449	0.504	0.898
R postcentral gyrus	0.572	0.450	0.655		0.667	0.415	0.751		0.014	0.905	0.956
R precentral gyrus	1.258	0.264	0.565		0.243	0.623	0.871		3.210	0.075	0.898
R precuneus	0.241	0.624	0.777		1.366	0.244	0.653		0.606	0.437	0.898
R straight gyrus	5.931	0.016	0.331	MDD < HC	0.232	0.630	0.871		0.408	0.524	0.898
R subcallosal gyrus	1.887	0.171	0.518		0.169	0.681	0.908		0.773	0.380	0.898
R anterior transverse temporal gyrus	0.007	0.933	0.985		7.122	0.008	0.281	CC > CT + TT	0.134	0.714	0.943
R lateral superior temporal gyrus	1.579	0.210	0.518		3.115	0.079	0.501		0.001	0.978	0.984
R planum polare	0.110	0.740	0.826		0.322	0.571	0.834		0.641	0.424	0.898
R planum temporale	3.537	0.062	0.362		5.203	0.024	0.359	CC > CT + TT	0.034	0.854	0.943
R inferior temporal gyrus	1.528	0.218	0.518		1.158	0.283	0.673		1.054	0.306	0.898
R middle temporal gyrus	1.545	0.215	0.518		0.038	0.845	0.939		0.178	0.674	0.931
Subcortical volume											
L thalamus	1.614	0.205	0.719		2.215	0.138	0.387		0.438	0.509	0.794
L caudate nucleus	2.068	0.152	0.710		5.446	0.021	0.251	CC > CT + TT	0.408	0.524	0.794
L putamen	0.389	0.534	0.934		0.107	0.744	0.801		4.757	0.030	0.213
L globus pallidum	0.001	0.973	0.973		1.686	0.196	0.457		0.241	0.624	0.794
L hippocampus	0.100	0.753	0.973		0.903	0.343	0.499		0.269	0.604	0.794
L amygdala	0.861	0.355	0.828		2.219	0.138	0.387		0.019	0.890	0.890

L nucleus accumbens	0.166	0.684	0.973		0.275	0.601	0.764		0.830	0.363	0.794
R thalamus	4.193	0.042	0.587	MDD < HC	1.046	0.308	0.499		1.591	0.209	0.671
R caudate nucleus	2.210	0.139	0.710		4.468	0.036	0.251	CC > CT + TT	1.392	0.240	0.671
R putamen	0.008	0.928	0.973		0.870	0.352	0.499		5.806	0.017	0.213
R globus pallidum	0.601	0.439	0.878		3.189	0.076	0.353		0.411	0.522	0.794
R hippocampus	0.989	0.321	0.828		0.049	0.826	0.826		0.081	0.776	0.836
R amygdala	0.033	0.857	0.973		0.856	0.356	0.499		0.105	0.746	0.836
R nucleus accumbens	0.009	0.926	0.973		0.190	0.663	0.774		3.627	0.058	0.272

The F and P values were obtained using analysis of covariance (ANCOVA) adjusted for age, gender, education level, medication, and total intracranial volume as covariates

The false discovery rate (FDR) was applied in each analysis for multiple comparison correction, q < 0.05; cortical volume: 76 comparisons in both hemispheres, cortical thickness: 76 comparisons in both hemispheres; subcortical volume: 14 comparisons in both hemispheres.

*Regions that remained significant after the multiple comparison correction are marked with an asterisk.

MDD, major depressive disorder; HC, healthy controls; CC, CC genotype of rs1360780; CT + TT, CT or TT genotype of rs1360780; L, left hemisphere; R, right hemisphere. P_{uncorr}, uncorrected p-value; P_{corr}, FDR-corrected p-value.

Table S4. Summary of post-hoc analyses of gray-matter volumes or cortical thickness with significant diagnosis-by-genotype interactions in patients with major depressive disorder and healthy controls.

brain regions	**MDD (n = 114)**				**HC (n = 88)**			
	CC (n = 72)	CT + TT (n = 42)	F	P_{uncorr}	CC (n = 58)	CT + TT (n = 30)	F	P_{uncorr}
cortical volume								
L pars triangularis	2564.49 ± 613.39	2303.79 ± 559.81	9.353	0.003	2575.86 ± 571.00	2750.63 ± 597.15	3.437	0.067
L supramarginal gyrus	6690.22 ± 1204.64	6168.60 ± 1276.03	11.172	0.001	6569.19 ± 1126.12	6809.53 ± 820.78	1.885	0.173
L superior parietal lobule	6393.49 ± 1089.78	5872.24 ± 804.03	14.819	<0.001	6207.41 ± 932.16	6423.77 ± 876.62	2.144	0.147
L posterior mid-cingulate gyrus	2628.75 ± 448.17	2557.38 ± 377.95	3.732	0.056	2608.38 ± 427.79	2775.50 ± 484.42	5.113	0.026
R frontomarginal gyrus	1721.94 ± 330.36	1583.38 ± 315.56	9.815	0.002	1715.86 ± 337.46	1800.43 ± 342.20	1.591	0.211

Data are mean ± standard deviation (mm^3).

Only cortical regions with significant diagnosis-by-genotype interactions after the multiple comparison correction are included in the table (FDR-corrected $P < 0.05$).

The F and P values were obtained using analysis of covariance (ANCOVA) adjusted for age, gender, education level, medication, and total intracranial volume as covariates

MDD, major depressive disorder; HC, healthy controls; CC, CC genotype of rs1360780; CT + TT, CT or TT genotype of rs1360780; L, left hemisphere; R, right hemisphere; $P_{uncorr,}$ uncorrected p-value.

Table S5. Post-hoc analysis of cortical volumes with significant diagnosis-by-genotype interactions in patients with major depressive disorder and healthy controls.

Cortical regions	**MDD (n = 114)**				**HC (n = 88)**			
	CC (n = 72)	CT + TT (n = 42)	F	P_{uncorr}	CC (n = 58)	CT + TT (n = 30)	F	P_{uncorr}
L pars triangularis	2564.49 ± 613.39	2303.79 ± 559.81	9.353	0.003	2575.86 ± 571.00	2750.63 ± 597.15	3.437	0.067
L short insular gyrus	2061.24 ± 339.47	2009.71 ± 306.35	4.299	0.041	2153.90 ± 359.80	2222.77 ± 273.86	0.918	0.341
L middle occipital gyrus	4827.39 ± 867.23	4655.98 ± 715.51	4.049	0.047	4960.03 ± 904.58	5176.83 ± 963.02	1.605	0.209
L supramarginal gyrus	6690.22 ± 1204.64	6168.60 ± 1276.03	11.172	0.001	6569.19 ± 1126.12	6809.53 ± 820.78	1.885	0.173
L superior parietal lobule	6393.49 ± 1089.78	5872.24 ± 804.03	14.819	<0.001	6207.41 ± 932.16	6423.77 ± 876.62	2.144	0.147
L precuneus	5857.99 ± 973.70	5624.14 ± 731.20	6.956	0.010	5743.05 ± 1010.20	5905.17 ± 675.48	0.927	0.339
L posterior mid-cingulate gyrus	2628.75 ± 448.17	2557.38 ± 377.95	3.732	0.056	2608.38 ± 427.79	2775.50 ± 484.42	5.113	0.026
R frontomarginal gyrus	1721.94 ± 330.36	1583.38 ± 315.56	9.815	0.002	1715.86 ± 337.46	1800.43 ± 342.20	1.591	0.211
R transverse frontopolar gyrus	2310.22 ± 406.80	2163.14 ± 405.36	4.688	0.033	2270.14 ± 357.84	2361.30 ± 454.03	1.252	0.266
R dorsal posterior cingulate gyrus	1432.22 ± 336.10	1375.24 ± 323.90	3.974	0.049	1403.14 ± 303.86	1478.63 ± 332.67	1.914	0.170
R middle occipital gyrus	5291.47 ± 1090.42	4997.19 ± 941.62	8.417	0.005	5298.98 ± 931.80	5379.43 ± 933.44	0.535	0.466
R orbital gyrus	5980.08 ± 877.20	5722.10 ± 889.00	8.279	0.005	6046.02 ± 812.76	6022.37 ± 723.25	0.049	0.826
R superior parietal lobule	4902.31 ± 762.04	4623.38 ± 756.98	6.965	0.010	4969.45 ± 818.88	4928.53 ± 609.30	0.001	0.972
R precuneus	5748.88 ± 951.95	5502.71 ± 817.23	7.430	0.007	5757.43 ± 898.57	5879.60 ± 937.58	0.606	0.438
R straight gyrus	1655.61 ± 267.93	1606.14 ± 266.42	4.070	0.046	1713.90 ± 259.79	1800.77 ± 295.04	3.335	0.071

Data are mean ± standard deviation (mm^3).

Only cortical regions with significant diagnosis-by-genotype interactions (uncorrected p-value < 0.05) in the main-analysis are included in the table.

The F and P values were obtained using analysis of covariance (ANCOVA) adjusted for age, gender, education level, medication, and total intracranial volume as covariates

MDD, major depressive disorder; HC, healthy controls; CC, CC genotype of rs1360780; CT + TT, CT or TT genotype of rs1360780; L, left hemisphere; R, right hemisphere; $P_{uncorr,}$ uncorrected P value.

Table S6. Post-hoc analysis of subcortical volumes with significant diagnosis-by-genotype interactions in patients with major depressive disorder and healthy controls.

Subcortical regions	**MDD (n = 114)**				**HC (n = 88)**			
	CC (n = 72)	CT + TT (n = 42)	F	P_{uncorr}	CC (n = 58)	CT + TT (n = 30)	F	P_{uncorr}
L putamen	5141.98 ± 710.80	5106.15 ± 543.83	2.725	0.102	5291.62 ± 763.71	5447.75 ± 495.58	1.821	0.181
R putamen	5042.27 ± 681.64	4940.60 ± 560.81	5.049	0.027	5117.38 ± 739.21	5233.06 ± 442.46	1.144	0.288

Data are mean ± standard deviation (mm^3).

Only subcortical regions with significant diagnosis-by-genotype interactions (uncorrected p-value < 0.05) in the main-analysis are included in the table.

The F and P values were obtained using analysis of covariance (ANCOVA) adjusted for age, gender, education level, medication, and total intracranial volume as covariates

MDD, major depressive disorder; HC, healthy controls; CC, CC genotype of rs1360780; CT + TT, CT or TT genotype of rs1360780; L, left hemisphere; R, right hemisphere; $P_{uncorr,}$ uncorrected P value.

Table S7. Post-hoc analysis of cortical thickness with significant diagnosis-by-genotype interactions in patients with major depressive disorder and healthy controls.

Cortical regions	**MDD (n = 114)**				**HC (n = 88)**			
	CC (n = 72)	CT + TT (n = 42)	F	P_{uncorr}	CC (n = 58)	CT + TT (n = 30)	F	P_{uncorr}
L dorsal posterior cingulate gyrus	2.746 ± 0.176	2.677 ± 0.210	4.010	0.048	2.738 ± 0.169	2.815 ± 0.200	6.693	0.011
R dorsal posterior cingulate gyrus	2.800 ± 0.170	2.757 ± 0.175	2.581	0.111	2.795 ± 0.171	2.827 ± 0.167	3.128	0.081

Data are mean ± standard deviation (mm^3).

Only brain regions with significant diagnosis-by-genotype interactions (uncorrected p-value < 0.05) in the main-analysis are included in the post-hoc analysis.

The F and P values were obtained using analysis of covariance (ANCOVA) adjusted for age, gender, education level, medication, and total intracranial volume as covariates

MDD, major depressive disorder; HC, healthy controls; CC, CC genotype of rs1360780; CT + TT, CT or TT genotype of rs1360780; L, left hemisphere; R, right hemisphere; $P_{uncorr,}$ uncorrected P value.

Table S8. Difference in DNA methylation of the *FKBP5* gene among groups determined by genotype and diagnosis.

CpG	MDD (%, n = 104)	HC (%, n = 82)	**MDD vs. HC**		CC (%, n = 118)	CT + TT (%, n = 68)	**CC vs. CT + TT**		**Diagnosis x Genotype interaction**	
			F	p			F	p	F	p
pos 1	97.65 ± 2.57	97.10 ± 2.61	2.256	0.135	97.65 ± 2.18	96.98 ± 3.17	2.168	0.143	2.570	0.111
pos 2	90.62 ± 5.37	90.49 ± 3.05	0.324	0.570	90.88 ± 4.64	90.02 ± 4.20	1.228	0.269	1.094	0.297

Data are mean ± standard deviation (%).

The F and P values were obtained using analysis of covariance (ANCOVA) adjusted for age, gender, and medication.

MDD, major depressive disorder; HC, healthy controls; CC, participants with CC genotype of rs1360780; CT + TT, participants with CT or TT genotype of rs1360780.

Table S9. Exploratory analysis of DNA methylation of the *FKBP5* gene in groups determined by genotype and diagnosis.

CpG	**MDD (n = 104)**				**HC (n = 82)**			
	CC (n = 65)	CT + TT (n = 39)	F	p	CC (n = 53)	CT + TT (n = 29)	F	p
pos 1	98.07 ± 1.77	96.94 ± 3.44	6.236	0.014	97.13 ± 2.52	97.04 ± 2.82	<0.001	0.994
pos 2	91.13 ± 5.51	89.77 ± 5.08	2.133	0.147	90.57 ± 3.28	90.35 ± 2.64	0.164	0.686

Data are mean ± standard deviation (%).

The F and P values were obtained using analysis of covariance (ANCOVA) adjusted for age, gender, and medication.

MDD, major depressive disorder; HC, healthy controls; CC, participants with CC genotype of rs1360780; CT + TT, participants with CT or TT genotype of rs1360780.

Table S10. Correlation analysis between cortical gray-matter volume and DNA methylation in intron 7 of the *FKBP5* gene among groups determined by diagnosis, genotype, and diagnosis-by-genotype interaction.

	Subgroups	**Regions**	**r or t**	**P_{uncorr}**	**CpG**
Diagnostic groups	MDD (n=104)	R subcallosal gyrus	-0.235	0.020	pos 1
	HC (n=82)	L dorsal posterior cingulate gyrus	-0.412	<0.001	pos 1
		R paracentral lobule	0.228	0.046	pos 2
		R pars orbitalis	0.290	0.011	pos 2
		R middle frontal gyrus	-0.233	0.041	pos 1
		R parahippocampal gyrus	-0.338	0.003	pos 2
		R precuneus	-0.247	0.030	pos 2
		R straight gyrus	0.286	0.012	pos 2
Genotype groups	T (n= 68)	L middle frontal gyrus	-0.276	0.030	pos 2
		L superior frontal gyrus	-0.258	0.043	pos 1
		L suparmarginal gyrus	-0.291	0.022	pos 1
		L suparmarginal gyrus	-0.401	0.001	pos 2
		L precental gyrus	-0.256	0.045	pos 1
		L precuneus	-0.322	0.011	pos 1
		L precuneus	-0.382	0.002	pos 2
		L straight gyrus	-0.252	0.048	pos 1
		L middle temporal gyrus	-0.263	0.039	pos 1
		L middle temporal gyrus	-0.267	0.036	pos 2
		R subcentral gyrus	-0.307	0.015	pos 1
		R dorsal posterior cingulate gyrus	-0.283	0.026	pos 1
		R dorsal posterior cingulate gyrus	-0.290	0.022	pos 2
		R pars orbitalis	-0.288	0.023	pos 1
		R parahippocampal gyrus	-0.312	0.013	pos 2
		R precuneus	-0.287	0.024	pos 2
		R subcallosal gyrus	-0.360	0.004	pos 2
		R inferior temporal gyrus	-0.258	0.043	pos 1
	CC (n= 118)	L angular gyrus	0.202	0.033	pos 1
		L precental gyrus	0.193	0.042	pos 1
		R frontomarginal gyrus	0.186	0.049	pos 1
		R straight gyrus	0.218	0.021	pos 1
		R subcallosal gyrus	-0.216	0.022	pos 1
		R middle temporal gyrus	0.190	0.044	pos 1

Interaction effect	Diagnosis × methylation	L dorsal posterior cingulate gyrus	2.303	0.022	pos 1
		L parahippocampal gyrus	2.157	0.032	pos 2
		R paracentral lobule	-2.029	0.044	pos 2
		R pars orbitalis	-2.201	0.029	pos 2
		R middle frontal gyrus	2.556	0.011	pos 1
		R parahippocampal gyrus	2.461	0.015	pos 2
		R precuneus	2.000	0.047	pos 2
	Genotype × methylation	L angular gyrus	-2.137	0.034	pos 1
		L supramarginal gyrus	-2.311	0.022	pos 2
		L precentral gyrus	-3.079	0.002	pos 1
		L straight gyrus	-2.169	0.031	pos 1
		R subcentral gyrus	-2.900	0.004	pos 1
		R pars orbitalis	-2.777	0.006	pos 1
		R straight gyrus	-2.494	0.014	pos 1
		R subcallosal gyrus	-2.165	0.032	pos 2
		R middle temporal gyrus	-2.231	0.027	pos 1
	Diagnosis × genotype × methylation	L pars opercularis	-2.114	0.036	pos 2
		L precentral gyrus	-2.286	0.023	pos 2
		L planum polare	-2.061	0.041	pos 2
		R inferior occipital gyrus	-2.558	0.011	pos 1
		R superior frontal gyrus	-2.087	0.038	pos 1
		R angular gyrus	-2.397	0.018	pos 1
		R precuneus	-2.100	0.037	pos 1
		R precuneus	-2.475	0.014	pos 2

A two-tailed Pearson's partial correlation was performed to analyze the correlations between the cortical volumes and percentage of *FKBP5* gene DNA methylation adjusting for following covariates according to each analysis: MDD group: age, gender, education level, medication, total intracranial cavity volume, and *FKBP5* genotype; HC group: age, gender, education level, total intracranial cavity volume, and *FKBP5* genotype; T or CC group: age, gender, education level, medication, total intracranial cavity volume, and diagnosis.

A hierarchical moderated regression analysis was performed to investigated the interactive effect of the DNA methylation with the diagnosis, genotype, or both diagnosis and genotype in terms of the correlation with the cortical volumes.

Only regions with statistically significant correlations are shown ($P_{uncorr} < 0.05$). No cortical regions remained significant after the multiple comparison correction ($P_{corr} > 0.05$).

The FDR was applied in each analysis for multiple comparison correction, q < 0.05; for diagnosis effect (MDD or HC group): 304 comparisons (=38 cortical regions x 2 hemispheres x 2 diagnosis groups x 2 CpG sites); genotype effect (T allele carrier or C homozygote group): 304 comparisons (=38 cortical regions x 2 hemispheres x 2 genotype groups x 2 CpG sites); and interactive effects (e.g. diagnosis-by-methylation, genotype-by-methylation, diagnosis-by-genotype-by-methylation): 456 comparisons (=38 cortical regions x 2 hemispheres x 3 interactions x 2 CpG sites).

The r-values for Pearson's partial correlation analyses and t-value for the hierarchical moderated regression analyses.

MDD, patients with major depressive disorder; HC, healthy controls; MDD-T, MDD patients with T allele of rs1360780; MDD-CC, MDD patients with CC genotype of rs1360780; L, left hemisphere; R, right hemisphere; $P_{uncorr,}$ uncorrected P value.

Table S11. Correlation analysis between subcortical gray-matter volume and DNA methylation in intron 7 of the *FKBP5* gene among groups determined by diagnosis, genotype, and diagnosis-by-genotype interaction.

	Subgroups	**Regions**	**r or t**	**P_{uncorr}**	**CpG**
Diagnostic groups	HC (n=82)	R globus pallidum	-0.240	0.035	pos 2
		R hippocampus	-0.226	0.048	pos 2
Genotype groups	T (n= 68)	R amygdala	-0.269	0.034	pos 1
	CC (n= 118)	L Caudate nucleus	0.198	0.037	pos 1
Interaction effect	Diagnosis × genotype × methylation	R thalamus	-2.484	0.014	pos 1

A two-tailed Pearson's partial correlation was performed to analyze the correlations between the subcortical volumes and percentage of *FKBP5* gene DNA methylation adjusting for following covariates according to each analysis: MDD group: age, gender, education level, medication, total intracranial cavity volume, and *FKBP5* genotype; HC group: age, gender, education level, total intracranial cavity volume, and *FKBP5* genotype; T or CC group: age, gender, education level, medication, total intracranial cavity volume, and diagnosis.

A hierarchical moderated regression analysis was performed to investigated the interactive effect of the DNA methylation with the diagnosis, genotype, or both diagnosis and genotype in terms of the correlation with the subcortical volumes.

Only regions with statistically significant correlations are shown ($P_{uncorr} < 0.05$). No subcortical regions remained significant after the multiple comparison correction ($P_{corr} > 0.05$).

The FDR was applied in each analysis for multiple comparison correction, q < 0.05; for diagnosis effect: 56 comparisons (=7 subcortical regions x 2 hemispheres x 2 diagnosis groups x 2 CpG sites); genotype effect: 56 comparisons (=7 subcortical regions x 2 hemispheres x 2 genotype groups x 2 CpG sites); and interactive effects: 84 comparisons (=7 subcortical regions x 2 hemispheres x 3 interactions x 2 CpG sites).

The r-values for Pearson's partial correlation analyses and t-value for the hierarchical moderated regression analyses.

MDD, patients with major depressive disorder; HC, healthy controls; MDD-T, MDD patients with T allele of rs1360780; MDD-CC, MDD patients with CC genotype of rs1360780; L, left hemisphere; R, right hemisphere; $P_{uncorr,}$ uncorrected P value.

Table S12. Correlation analysis between cortical thickness and DNA methylation in intron 7 of the *FKBP5* gene among groups determined by diagnosis, genotype, and diagnosis-by-genotype interaction.

	Subgroups	**Regions**	**r**	**P_{uncorr}**	**CpG**
Diagnostic groups	MDD (n=104)	L inferior occipital gyrus	0.253	0.012	pos 1
		L transverse frontopolar gyrus	0.246	0.015	pos 1
		L dorsal posterior cingulate gyrus	0.215	0.033	pos 1
		L middle occipital gyrus	0.281	0.005	pos 1
		L superior occipital gyrus	0.230	0.023	pos 1
		L lingual gyrus	0.205	0.043	pos 1
		L angular gyrus	0.206	0.042	pos 1
		L precuneus	0.210	0.038	pos 1
		R frontomarginal gyrus	0.248	0.014	pos 1
		R middle occipital gyrus	0.209	0.039	pos 1
		R angular gyrus	0.217	0.032	pos 1
	HC (n=82)	L pars opercularis	0.307	0.007	pos 1
		L fusiform gyrus	0.251	0.028	pos 1
		L suparmarginal gyrus	0.225	0.049	pos 1
		L inferior temporal gyrus	0.303	0.007	pos 1
		R inferior occipital gyrus	0.234	0.041	pos 1
		R pars opercularis	0.266	0.020	pos 1
		R fusiform gyrus	0.271	0.017	pos 1
		R postcentral gyrus	0.231	0.043	pos 1
		R subcallosal gyrus	-0.282	0.013	pos 1
		R inferior temporal gyrus	0.241	0.035	pos 1
		R middle temporal gyrus	0.256	0.025	pos 1
Genotype groups	T (n= 68)	L subcentral gyrus	-0.259	0.042	pos 1
		R frontomarginal gyrus	0.271	0.033	pos 2
		R ventral posterior cingulate gyrus	0.352	0.005	pos 1
		R ventral posterior cingulate gyrus	0.305	0.016	pos 2
	CC (n= 118)	L pars opercularis	0.258	0.006	pos 1
		L middle frontal gyrus	-0.190	0.044	pos 2
		L superior frontal gyrus	0.257	0.006	pos 1
		L middle occipital gyrus	0.247	0.009	pos 1
		L superior occipital gyrus	0.239	0.011	pos 1
		L fusiform gyrus	0.269	0.004	pos 1
		L parahippocampal gyrus	0.255	0.007	pos 1

		L angular gyrus	0.282	0.003	pos 1
		L angular gyrus	-0.247	0.009	pos 2
		L supramarginal gyrus	0.216	0.022	pos 1
		L supramarginal gyrus	-0.229	0.015	pos 2
		L superior parietal lobule	-0.231	0.014	pos 2
		L precuneus	0.207	0.028	pos 1
		L precuneus	-0.220	0.020	pos 2
		L inferior temporal gyrus	0.210	0.026	pos 1
		L middle temporal gyrus	0.213	0.024	pos 1
		R inferior occipital gyrus	0.244	0.010	pos 1
		R paracentral lobule	0.191	0.044	pos 1
		R transverse frontopolar gyrus	0.353	**<0.001***	pos 1
		R pars opercularis	0.291	0.002	pos 1
		R pars orbitalis	0.235	0.013	pos 1
		R superior frontal gyrus	0.288	0.002	pos 1
		R short insular gyrus	0.253	0.007	pos 1
		R middle occipital gyrus	0.309	0.001	pos 1
		R fusiform gyrus	0.298	0.001	pos 1
		R orbital gyrus	0.266	0.005	pos 1
		R angular gyrus	0.197	0.038	pos 1
		R supramarginal gyrus	-0.203	0.032	pos 2
		R precentral gyrus	0.198	0.037	pos 1
		R precuneus	-0.271	0.004	pos 2
		R lateral superior temporal gyrus	0.210	0.027	pos 1
		R inferior temporal gyrus	0.215	0.023	pos 1
		R middle temporal gyrus	0.315	0.001	pos 1
Interaction effects	Diagnosis × methylation	L frontomarginal gyrus	2.675	0.008	pos 1
		L inferior occipital gyrus	2.181	0.031	pos 1
		L dorsal posterior cingulate gyrus	2.202	0.029	pos 1
		R subcallosal gyrus	2.016	0.045	pos 1
	Genotype × methylation	L transverse frontopolar gyrus	2.632	0.009	pos 2
		L pars triangularis	2.435	0.016	pos 2
		L superior occipital gyrus	2.245	0.026	pos 2
		L lingual gyrus	2.480	0.014	pos 2
		L angular gyrus	-2.061	0.041	pos 1
		L angular gyrus	2.351	0.020	pos 2
		L supramarginal gyrus	2.152	0.033	pos 2

		L postcentral gyrus	2.605	0.010	pos 2
		L precentral gyrus	-2.148	0.033	pos 1
		L middle temporal gyrus	2.132	0.034	pos 2
		R frontomarginal gyrus	2.804	0.006	pos 2
		R transverse frontopolar gyrus	-2.486	0.014	pos 1
		R ventral posterior cingulate gyrus	2.308	0.022	pos 1
		R ventral posterior cingulate gyrus	3.142	0.002	pos 2
		R pars opercularis	-2.099	0.037	pos 1
		R pars orbitalis	-2.785	0.006	pos 1
		R superior frontal gyrus	-2.063	0.041	pos 1
		R short insular gyrus	-2.086	0.038	pos 1
		R middle occipital gyrus	2.231	0.027	pos 2
		R fusiform gyrus	-2.080	0.039	pos 1
		R orbital gyrus	-2.213	0.028	pos 1
		R precentral gyrus	-2.319	0.022	pos 1
	Diagnosis × genotype × methylation	L supramarginal gyrus	-2.323	0.021	pos 1

A two-tailed Pearson's partial correlation was performed to analyze the correlations between the cortical thickness and percentage of *FKBP5* gene DNA methylation adjusting for following covariates according to each analysis: MDD group: age, gender, education level, medication, total intracranial cavity volume, and *FKBP5* genotype; HC group: age, gender, education level, total intracranial cavity volume, and *FKBP5* genotype; T or CC group: age, gender, education level, medication, total intracranial cavity volume, and diagnosis.

A hierarchical moderated regression analysis was performed to investigated the interactive effect of the DNA methylation with the diagnosis, genotype, or both diagnosis and genotype in terms of the correlation with the cortical thickness.

Only regions with statistically significant correlations are shown ($P_{uncorr} < 0.05$).

*Regions that remained significant after the multiple comparison correction are marked with an asterisk.

The FDR was applied in each analysis for multiple comparison correction, q < 0.05; for diagnosis effect (MDD or HC group): 304 comparisons (=38 cortical regions x 2 hemispheres x 2 diagnosis groups x 2 CpG sites); genotype effect (T allele carrier or C homozygote group): 304 comparisons (=38 cortical regions x 2 hemispheres x 2 genotype groups x 2 CpG sites); and interactive effects (e.g. diagnosis-by-methylation, genotype-by-methylation, diagnosis-by-genotype-by-methylation): 456 comparisons (=38 cortical regions x 2 hemispheres x 3 interactions x 2 CpG sites).

The r-values for Pearson's partial correlation analyses and t-value for the hierarchical moderated regression analyses.

MDD, patients with major depressive disorder; HC, healthy controls; MDD-T, MDD patients with T allele of rs1360780; MDD-CC, MDD patients with CC genotype of rs1360780; L, left hemisphere; R, right hemisphere;

$P_{uncorr,}$ uncorrected P value.

Table S13. Exploratory analysis investigating effect of diagnosis, genotype, and diagnosis-by-genotype interaction on cortical surface area of whole-brain.

brain regions	MDD vs. HC			CC vs. CT + TT			Diagnosis x Genotype interaction		
	F	P_{uncorr}	P_{corr}	F	P_{uncorr}	P_{corr}	F	P_{uncorr}	P_{corr}
Cortical surface area									
L frontomarginal gyrus	0.223	0.638	0.905	1.860	0.174	0.977	0.858	0.355	0.808
L inferior occipital gyrus	0.034	0.853	0.958	0.049	0.826	0.977	4.023	0.046	0.354
L paracentral lobule	3.109	0.079	0.549	0.544	0.461	0.977	0.531	0.467	0.808
L subcentral gyrus	0.064	0.801	0.947	2.146	0.145	0.977	0.035	0.851	0.951
L transverse frontopolar gyrus	1.655	0.200	0.758	0.073	0.787	0.977	1.681	0.196	0.711
L anterior cingulate gyrus	0.326	0.569	0.905	0.096	0.757	0.977	0.676	0.412	0.808
L anterior midcingulate gyrus	0.750	0.388	0.866	0.064	0.800	0.977	0.225	0.636	0.838
L posterior midcingulate gyrus	1.096	0.297	0.758	0.913	0.340	0.977	0.373	0.542	0.808
L dorsal posterior cingulate gyrus	3.459	0.064	0.549	1.804	0.181	0.977	4.010	0.047	0.354
L ventral posterior cingulate gyrus	1.340	0.248	0.758	0.216	0.643	0.977	0.469	0.494	0.808
L cuneus	1.252	0.265	0.758	0.152	0.697	0.977	0.607	0.437	0.808
L pars opercularis	0.976	0.324	0.771	0.045	0.833	0.977	0.449	0.503	0.808
L pars orbitalis	0.136	0.713	0.919	0.744	0.389	0.977	0.193	0.661	0.838
L pars triangularis	0.087	0.769	0.928	0.025	0.874	0.977	5.915	0.016	0.303
L middle frontal gyrus	0.173	0.678	0.905	0.104	0.748	0.977	0.052	0.819	0.951

L superior frontal gyrus	0.001	0.973	0.986		0.025	0.874	0.977		8.542	0.004	0.126
L long insular gyrus	0.486	0.486	0.905		0.012	0.914	0.979		1.209	0.273	0.808
L short insular gyrus	0.811	0.369	0.850		2.741	0.099	0.977		0.784	0.377	0.808
L middle occipital gyrus	3.974	0.048	0.549	MDD < HC	1.611	0.206	0.977		2.051	0.154	0.678
L superior occipital gyrus	2.618	0.107	0.627		0.222	0.638	0.977		2.236	0.136	0.678
L lateral occipito-temporal gyrus	0.007	0.933	0.958		0.233	0.630	0.977		0.571	0.451	0.808
L lingual gyrus	0.361	0.549	0.905		0.092	0.762	0.977		0.010	0.922	0.982
L parahippocampal gyrus	2.213	0.138	0.702		0.699	0.404	0.977		0.633	0.427	0.808
L orbital gyrus	7.066	0.009	0.351	MDD > HC	0.072	0.789	0.977		0.010	0.921	0.982
L angular gyrus	6.914	0.009	0.351	MDD > HC	1.754	0.187	0.977		1.009	0.316	0.808
L supramarginal gyrus	0.010	0.920	0.958		0.089	0.765	0.977		4.568	0.034	0.354
L superior parietal lobule	1.309	0.254	0.758		0.099	0.754	0.977		1.938	0.166	0.678
L postcentral gyrus	0.380	0.538	0.905		2.045	0.154	0.977		1.823	0.178	0.678
L precentral gyrus	0.000	0.991	0.991		2.273	0.133	0.977		4.277	0.040	0.354
L precuneus	0.650	0.421	0.905		0.002	0.961	0.987		0.582	0.446	0.808
L straight gyrus	0.012	0.913	0.958		0.271	0.603	0.977		0.328	0.567	0.816
L subcallosal gyrus	4.818	0.029	0.549	MDD > HC	0.623	0.431	0.977		0.859	0.355	0.808
L anterior transverse temporal gyrus	0.090	0.764	0.928		0.881	0.349	0.977		0.469	0.494	0.808
L lateral superior temporal gyrus	0.555	0.457	0.905		0.000	0.992	0.992		0.290	0.591	0.816
L planum polare	0.025	0.874	0.958		0.467	0.495	0.977		0.738	0.391	0.808
L planum temporale	1.341	0.248	0.758		0.000	0.991	0.992		0.005	0.942	0.982
L inferior temporal gyrus	1.124	0.290	0.758		1.124	0.290	0.977		0.102	0.750	0.920
L middle temporal gyrus	0.102	0.750	0.928		1.035	0.310	0.977		0.001	0.982	0.982
R frontomarginal gyrus	0.058	0.810	0.947		0.111	0.740	0.977		8.076	0.005	0.126

R inferior occipital gyrus	0.042	0.838	0.958		0.018	0.895	0.979		0.833	0.363	0.808
R paracentral lobule	2.948	0.088	0.555		0.007	0.932	0.979		0.001	0.976	0.982
R subcentral gyrus	2.047	0.154	0.728		8.608	0.004	0.167	CC > CT + TT	0.002	0.962	0.982
R transverse frontopolar gyrus	0.339	0.561	0.905		0.117	0.732	0.977		2.148	0.144	0.678
R anterior cingulate gyrus	0.274	0.601	0.905		0.006	0.941	0.979		0.077	0.782	0.944
R anterior midcingulate gyrus	0.264	0.608	0.905		0.637	0.426	0.977		1.116	0.292	0.808
R posterior midcingulate gyrus	0.189	0.664	0.905		2.322	0.129	0.977		4.973	0.027	0.354
R dorsal posterior cingulate gyrus	1.180	0.279	0.758		0.102	0.750	0.977		0.227	0.634	0.838
R ventral posterior cingulate gyrus	1.039	0.309	0.758		0.423	0.516	0.977		0.302	0.583	0.816
R cuneus	0.231	0.632	0.905		0.322	0.571	0.977		4.270	0.040	0.354
R pars opercularis	1.671	0.198	0.758		0.460	0.498	0.977		0.614	0.434	0.808
R pars orbitalis	0.239	0.626	0.905		0.007	0.933	0.979		0.872	0.352	0.808
R pars triangularis	0.566	0.453	0.905		8.312	0.004	0.167	CC < CT + TT	0.041	0.840	0.951
R middle frontal gyrus	3.139	0.078	0.549		0.223	0.638	0.977		0.035	0.851	0.951
R superior frontal gyrus	0.325	0.569	0.905		0.034	0.854	0.977		8.610	0.004	0.126
R long insular gyrus	0.173	0.678	0.905		0.774	0.380	0.977		0.004	0.952	0.982
R short insular gyrus	0.016	0.901	0.958		1.294	0.257	0.977		0.199	0.656	0.838
R middle occipital gyrus	0.366	0.546	0.905		0.239	0.625	0.977		3.085	0.081	0.557
R superior occipital gyrus	0.097	0.756	0.928		1.134	0.288	0.977		0.013	0.909	0.982
R lateral occipito-temporal gyrus	0.032	0.858	0.958		0.734	0.393	0.977		2.564	0.111	0.649
R lingual gyrus	0.350	0.555	0.905		1.411	0.236	0.977		0.214	0.644	0.838
R parahippocampal gyrus	5.233	0.023	0.549	MDD > HC	0.759	0.385	0.977		1.006	0.317	0.808
R orbital gyrus	0.014	0.905	0.958		0.390	0.533	0.977		1.362	0.245	0.808
R angular gyrus	3.257	0.073	0.549		0.272	0.603	0.977		0.376	0.541	0.808

R supramarginal gyrus	1.312	0.253	0.758		0.592	0.443	0.977		0.107	0.744	0.920
R superior parietal lobule	1.045	0.308	0.758		2.655	0.105	0.977		0.549	0.459	0.808
R postcentral gyrus	3.966	0.048	0.549	MDD < HC	0.868	0.353	0.977		0.872	0.352	0.808
R precentral gyrus	0.159	0.691	0.905		2.276	0.133	0.977		2.662	0.104	0.649
R precuneus	0.310	0.579	0.905		0.029	0.865	0.977		0.489	0.485	0.808
R straight gyrus	1.515	0.220	0.758		1.392	0.239	0.977		2.390	0.124	0.672
R subcallosal gyrus	3.385	0.067	0.549		0.355	0.552	0.977		0.053	0.818	0.951
R anterior transverse temporal gyrus	1.509	0.221	0.758		0.947	0.332	0.977		0.413	0.521	0.808
R lateral superior temporal gyrus	0.301	0.584	0.905		2.922	0.089	0.977		0.426	0.515	0.808
R planum polare	0.299	0.585	0.905		0.056	0.813	0.977		0.318	0.573	0.816
R planum temporale	1.963	0.163	0.728		1.010	0.316	0.977		1.844	0.176	0.678
R inferior temporal gyrus	2.282	0.133	0.702		0.332	0.565	0.977		1.324	0.251	0.808
R middle temporal gyrus	0.161	0.689	0.905		0.072	0.789	0.977		1.007	0.317	0.808

The F and P values were obtained using analysis of covariance (ANCOVA) adjusted for age, gender, education level, medication, and total cortical surface area as covariates

The false discovery rate (FDR) was applied in each analysis for multiple comparison correction, $q < 0.05$; cortical surface area: 76 comparisons in both hemispheres.

*Regions that remained significant after the multiple comparison correction are marked with an asterisk.

Cortical regions which had significant diagnosis-by-genotype interaction or genotype effect in the main analysis on the genotype are represented with bolded-face.

MDD, major depressive disorder; HC, healthy controls; CC, CC genotype of rs1360780; CT + TT, CT or TT genotype of rs1360780; L, left hemisphere; R, right hemisphere. P_{uncorr}, uncorrected p-value; P_{corr}, FDR-corrected p-value.

Table S14. Exploratory analysis investigating correlations between cortical surface area and DNA methylation in intron 7 of the *FKBP5* gene among groups determined by diagnosis, genotype, and diagnosis-by-genotype interaction.

	Subgroups	**Regions**	**r or t**	**P_{uncorr}**	**CpG**
Diagnostic groups	MDD (n=104)	L anterior midcingulate gyrus	0.215	0.034	pos 2
		L suparmarginal gyrus	-0.241	0.017	pos 1
		R inferior occipital gyrus	0.226	0.025	pos 1
		R middle frontal gyrus	0.281	0.005	pos 1
		R subcallosal gyrus	-0.239	0.018	pos 1
	HC (n=82)	L frontomarginal gyrus	0.242	0.034	pos 1
		L orbital gyrus	0.251	0.028	pos 1
		R dorsal posterior cingulate gyrus	0.233	0.041	pos 2
		R pars orbitalis	0.245	0.032	pos 2
		R short insular gyrus	-0.300	0.008	pos 1
		R parahippocampal gyrus	-0.267	0.019	pos 2
		R straight gyrus	0.229	0.046	pos 1
		R lateral superior temporal gyrus	0.229	0.045	pos 2
		R planum temporale	0.227	0.048	pos 2
Genotype groups	T (n= 68)	L anterior midcingulate gyrus	0.333	0.008	pos 2
		L posterior midcingulate gyrus	0.271	0.033	pos 2
		L ventral posterior cingulate gyrus	0.272	0.033	pos 1
		L fusiform gyrus	0.344	0.006	pos 2
		L supramarginal gyrus	-0.271	0.033	pos 1
		L supramarginal gyrus	-0.389	0.002	pos 2
		L precuneus	-0.260	0.042	pos 2
		L planum polare	0.253	0.048	pos 2
		R dorsal posterior cingulate gyrus	-0.253	0.047	pos 1
		R subcallosal gyrus	-0.314	0.013	pos 2
	CC (n= 118)	R subcentral gyrus	0.214	0.024	pos 1
		R short insular gyrus	-0.255	0.007	pos 1
		R middle occipital gyrus	-0.228	0.015	pos 1
		R superior occipital gyrus	-0.213	0.024	pos 1
		R rectus gyrus	0.193	0.041	pos 1
		R planum temporale	0.210	0.026	pos 1

Interaction effects	Diagnosis × methylation	R transverse frontopolar gyrus	2.211	0.028	pos 1
		R pars orbitalis	-2.215	0.028	pos 2
		R middle frontal gyrus	2.453	0.015	pos 1
		R short insular gyrus	2.562	0.011	pos 1
		R parahippocampal gyrus	2.079	0.039	pos 2
	Genotype × methylation	L middle frontal gyrus	-2.322	0.021	pos 2
		L supramarginal gyrus	-3.277	0.001	pos 2
		L superior parietal lobule	-2.080	0.039	pos 2
		L precuneus	-2.894	0.004	pos 2
		R frontomarginal gyrus	-2.289	0.023	pos 1
		R subcentral gyrus	-2.753	0.007	pos 1
		R dorsal posterior cingulate gyrus	-2.582	0.011	pos 2
		R middle occipital gyrus	2.054	0.041	pos 1
		R angular gyrus	-2.055	0.041	pos 2
		R precuneus	-2.088	0.038	pos 2
		R straight gyrus	-2.396	0.018	pos 1
		R subcallosal gyrus	-2.448	0.015	pos 2
	Diagnosis × genotype × methylation	L planum polare	-2.024	0.044	pos 1
		L planum polare	-2.360	0.019	pos 2
		R inferior occipital gyrus	-2.077	0.039	pos 1
		R superior frontal gyrus	-2.041	0.043	pos 1
		R precuneus	-2.010	0.046	pos 2

A two-tailed Pearson's partial correlation was performed to analyze the correlations between the cortical surface area and percentage of *FKBP5* gene DNA methylation adjusting for following covariates according to each analysis: MDD group: age, gender, education level, medication, total intracranial cavity volume, and *FKBP5* genotype; HC group: age, gender, education level, total intracranial cavity volume, and *FKBP5* genotype; T or CC group: age, gender, education level, medication, total intracranial cavity volume, and diagnosis.

A hierarchical moderated regression analysis was performed to investigated the interactive effect of the DNA methylation with the diagnosis, genotype, or both diagnosis and genotype in terms of the correlation with the cortical surface area.

Only regions with statistically significant correlations are shown ($P_{uncorr} < 0.05$). No cortical regions remained significant after the multiple comparison correction ($P_{corr} > 0.05$).

The FDR was applied in each analysis for multiple comparison correction, $q < 0.05$; for diagnosis effect (MDD or HC group): 304 comparisons (=38 cortical regions x 2 hemispheres x 2 diagnosis groups x 2 CpG sites); genotype effect (T allele carrier or C homozygote group): 304 comparisons (=38 cortical regions x 2 hemispheres x 2 genotype groups x 2 CpG sites); and interactive effects (e.g. diagnosis-by-methylation, genotype-by-methylation, diagnosis-by-genotype-by-methylation): 456 comparisons (=38 cortical regions x 2 hemispheres x 3 interactions x 2 CpG sites).

The r-values for Pearson's partial correlation analyses and t-value for the hierarchical moderated regression analyses.

MDD, patients with major depressive disorder; HC, healthy controls; MDD-T, MDD patients with T allele of rs1360780; MDD-CC, MDD patients with CC genotype of rs1360780; L, left hemisphere; R, right hemisphere; $P_{uncorr,}$ uncorrected P value.

Table S15. Differences in DNA methylation in intron 7 of the *FKBP5* gene between groups determined by antidepressant treatment.

CpG	Drug-naïve (%, n = 49)	ADT (%, n = 55)	**Drug-naïve vs. ADT**	
			F	p
pos 1	97.97 ± 2.02	97.36 ± 2.97	1.000	0.320
pos 2	91.11 ± 2.66	90.18 ± 6.95	0.506	0.479

Data are mean ± standard deviation (%).

The F and P values were obtained using analysis of covariance (ANCOVA) adjusted for age and gender.

Drug-naïve, Drug-naïve MDD patients; ADT, MDD patients with antidepressant treatment.