Supplementary Table S1: SNP marker information for the Clinical Brain Disorders Branch sample

SNP rs number	SNP label[a]	Coding Strand	Chromosome Location[b]	Intermarker distance	Controls: MAF[c]	Cases: MAF[c]	Pairwise D'
rs2498804		G/T	104304140	0	0.32	0.31	
							0.97
rs2494732	SNP5	A/G	104310237	6097	0.44	0.45	
							0.98
rs1130233[+]	SNP4	G/A	104310939	702	0.24	0.26	
							0.98
rs2494734		C/G	104311930	991	0.46	0.46	
							0.96
rs2494735		A/G	104314011	2081	0.37	0.36	
							0.82
rs2498794		T/C	104316296	2285	0.47	0.46	
							0.85
rs2494737		T/A	104317370	1074	0.31	0.30	
							0.92
rs3730358	SNP3	C/T	104317452	82	0.15	0.15	
							1.00
rs2494738		C/T	104317731	279	0.067	0.084	
							0.29
rs2494740		A/T	104318926	1195	0.31	0.30	
							0.16
rs10149779	SNP2a	C/T	104322131	3205	0.32	0.29	
							0.98
rs1130214	SNP2	G/T	104330779	8648	0.29	0.30	
							0.77
rs3803300	SNP1	G/A	104340824	10045	0.084	0.01	

[a] According to labels by Emamian et al (1) and Schwab et al (2).
[b] According to UCSC Genome Browser Mar 2006 assembly
[c] MAF: minor allele frequency
[+] rs1130233 was formerly rs2498799 in the earlier literature

Supplementary Table S2: Exploratory analysis of *AKT1* association with cognitive factor 4 with denser SNP map (n=319 healthy individuals).

rs number	rs2498804	rs2494732	rs1130233[+]	rs2494734	rs2494735	rs2498794	rs2494737	rs3730358	rs2494738	rs2494740	rs10149779	rs1130214	rs3803300		p-value	Global p-value
SNP label by Emamian et al. (1) and Schwab et al. (2)		snp5	snp4					snp3			snp2a	snp2	snp1			
Cognitive Factor 4																
IQ/processing speed																
	G	G	G											↑	0.005	
	G	G	A											↓	0.0057	0.012
	T	G	A											↓	0.012	
		G	A	G										↓	0.0010	0.0040**
		G	G	C										↑	0.011	
			A	G	A									↓	0.0017	0.0046
			A	G	G									↓	0.023	
			A*											↓	0.003	
Coding Strand	G/T	A/G	G/A	C/G	A/G	T/C	T/A	C/T	C/T	A/T	C/T	G/T	G/A			

[+] rs1130233 was formerly rs2498799 in the earlier literature

Shaded blocks denote 3-SNP sliding window haplotypes associated with factor 4 at an exploratory global $p<0.05$.

↑ denotes association with increased scores; ↓ denotes association with decreased scores.

** denotes 3-SNP haplotype with global $p<0.05$ corrected for the 11 haplotypes tested.

*denote single SNP within the most significant haplotype that was $p<0.05$ corrected for the 3 SNPs tested.

Supplementary Table S3: Demographic characteristics of subjects

	Lymphoblast study (n=32)		First fMRI study (n=46)		Second fMRI study (n=68)		Structural MRI study (n=171)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age, yrs	31.75	10.05	30.72	7.84	32.15	9.29	34.04	9.87
Gender, no. male	14	-	16	-	37	-	77	-
Education, yrs	16.91	2.58	16.62	2.54	17.01	2.74	17.08	2.90
WAIS IQ	108.3	2.58	108.7	9.28	107.5	8.95	108.4	8.76
AKT1 G-allele frequency[+]	0.79	-	0.75	-	0.74	-	0.78	-
AKT1 A-allele frequency[+]	0.21	-	0.25	-	0.26	-	0.22	-
COMT Val-allele frequency	0.52	-	0.49	-	0.51	-	0.52	-
COMT Met-allele frequency	0.48	-	0.51	-	0.49	-	0.48	-

[+] rs1130233 (formerly rs2498799 in the earlier literature).

Supplementary Table S4: Behavioral performance across groups of subjects during 2-back fMRI according to genotype.

	First fMRI study (n=46)		Second fMRI study (n=68)	
	Mean	SD	Mean	SD
Accuracy (*AKT* GG/ A)[+]	0.866/ 0.893	0.101/ 0.084	0.805/ 0.750	0.162/ 0.124
Reaction time, sec (*AKT* GG/ A)[+]	0.458/ 0.513	0.172/ 0.262	0.561/ 0.543	0.237/ 0.235
Accuracy (*COMT* VV/M)	0.874/ 0.882	0.105/ 0.084	0.839/ 0.799	0.151/ 0.147
Reaction time, sec (*COMT* VV/M)	0.541/ 0.430	0.244/ 0.178	0.567/ 0.549	0.241/ 0.235

[+]rs1130233 (formerly rs2498799 in the earlier literature)
VV: *COMT*-Val homozygotes; M: *COMT*-Met carriers; GG: *AKT1* rs1130233 G-homozygotes; A: *AKT1* rs1130233 A-carriers.
Behavioral performance differences across genotypes for each study (*AKT* GG vs A, or *COMT* VV vs M) were all $p>0.1$.

Supplementary Table S5: Brain regions activated by the working memory task (2-back vs. 0-back), thresholded at $p<0.05$ corrected for false discovery rate (FDR) in the whole brain search volume.

Region	BA	Coordinates	t	z
L middle frontal gyrus*	9/46	-38 49 24	14.14	Not calc
L middle frontal gyrus	6	-41 8 54	13.91	Not calc
R inferior parietal lobule	40	49 -49 48	13.65	Not calc
L superior parietal lobule	7	-30 -68 48	13.34	Not calc
R inferior frontal gyrus	47	34 26 -6	13.32	Not calc
L inferior frontal gyrus	47	-30 26 -6	13.27	Not calc
L middle frontal gyrus	6	-26 8 60	13.20	Not calc
L superior frontal gyrus	6	-4 19 54	13.17	Not calc
L precuneus	7	-4 -64 54	13.13	Not calc
L inferior parietal lobule	40	-38 -52 42	12.82	Not calc
R middle frontal gyrus*	9	41 4 42	12.42	Not calc
R inferior frontal gyrus*	9	45 8 36	12.24	Not calc
R superior parietal lobule	7	11 -68 54	12.16	Not calc
L middle frontal gyrus*	9	-49 19 36	11.54	7.81
L caudate		-15 0 12	11.51	7.80
L inferior frontal gyrus*	45	-49 15 6	11.37	7.75
R middle frontal gyrus	8	-34 30 48	11.15	7.68
R middle frontal gyrus	6	30 4 60	11.13	7.67
R precuneus	19	26 -71 42	10.93	7.60
L medial frontal gyrus	8	-8 34 36	10.78	7.54
R inferior frontal gyrus*	44	52 15 6	10.46	7.41
L globus pallidus		-11 -4 -6	10.43	7.40
R cerebellum		34 -64 -42	10.42	7.39
R middle frontal gyrus*	9	49 30 30	10.15	7.28
R caudate		19 -4 18	9.34	6.93
R middle frontal gyrus*	46	41 45 24	9.14	6.84
L inferior temporal lobe	37	-49 -52 -12	9.13	6.83
L cerebellum		-26 -64 -42	8.64	6.60
R superior temporal gyrus	22	60 -49 12	8.44	6.50

BA: Brodmann Area, t: t-statistic, z: z-statistic

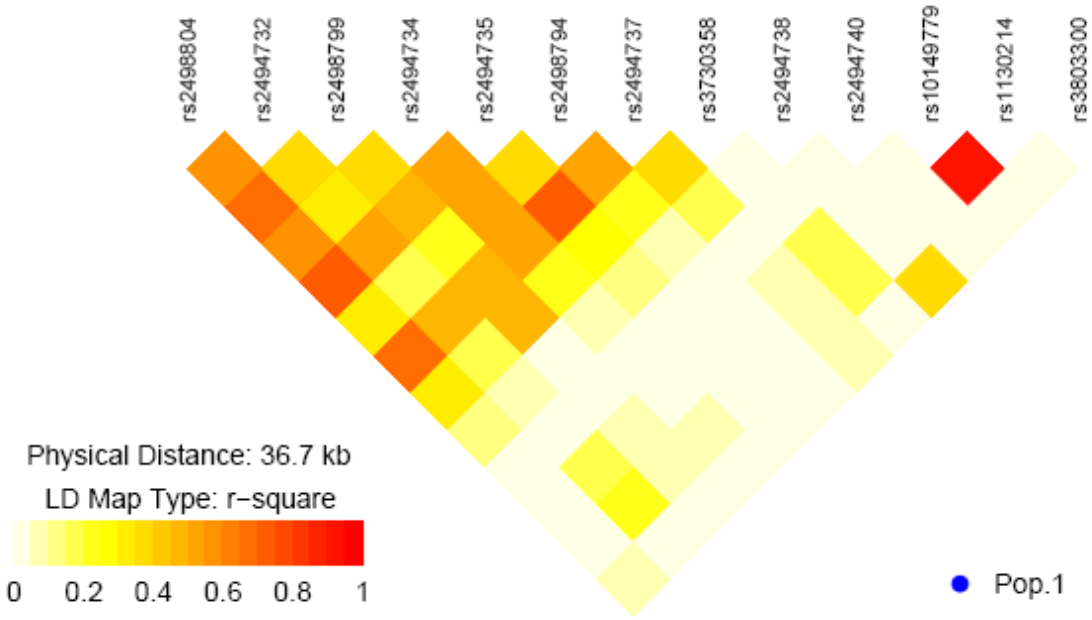
*refers to contiguous regions anatomically in the prefrontal cortex region-of-interest in which gene effects were interrogated.

Supplementary Table S6: Brain regions showing *AKT1* rs1130233 GG>A gray-matter volumes in the structural MRI study (n=171) thresholded at p<0.001 uncorrected.

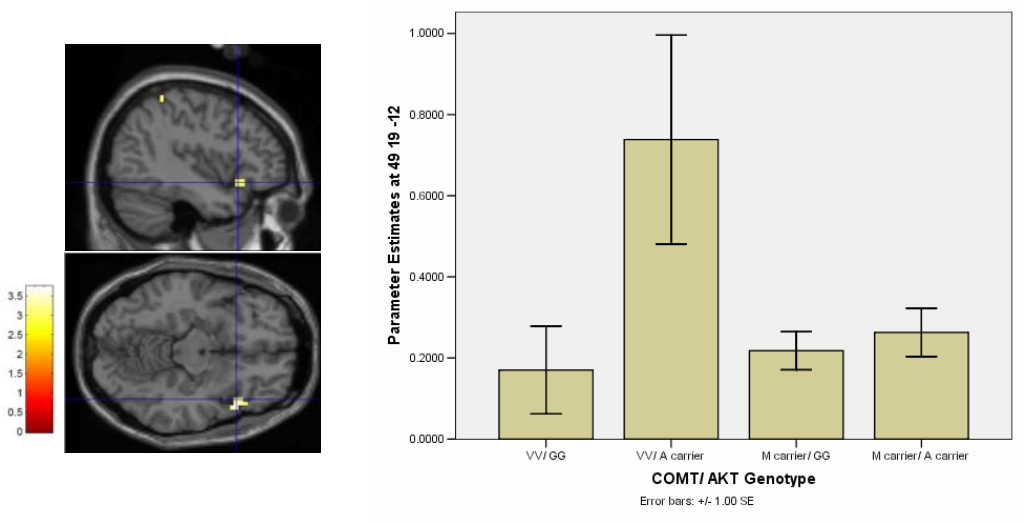
Region	BA	Coordinates	t	z
R Inferior frontal gyrus	47	37 18 -12	3.82	3.73*
L putamen	-	-10 7 3	3.89	3.79*
R putamen	-	12 7 4	3.44	3.37*
L paracentral lobule	24	-16 -15 49	4.30	4.18
R precentral gyrus	4	22 -19 57	3.50	3.44
L middle frontal gyrus	10	-31 51 6	3.44	3.37
R medial frontal gyrus	10	12 56 21	3.43	3.36

BA: Brodmann Area, t: t-statistic, z: z-statistic

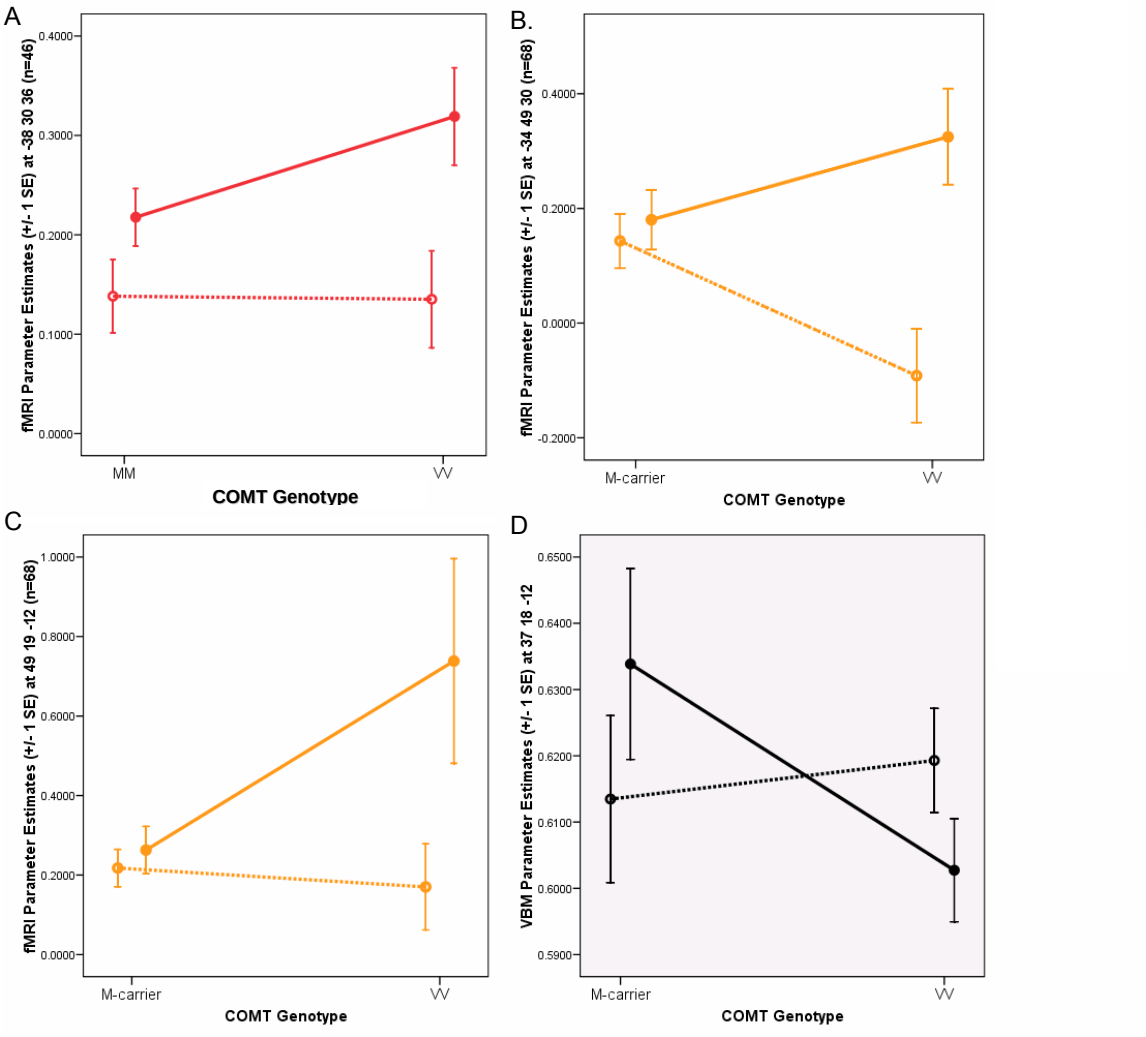
*survived p≤0.05 FDR correction within prefrontal-striatal region-of-interest



Supplementary Figure S1: Linkage disequilibrium (LD) across 13 *AKT1* SNPs in the sample of healthy individuals (n=370). Prepared using snp.plotter(3). rs2498799 in the earlier literature is now re-labeled rs1130233.



Supplementary Figure S2: Exploratory analysis on second fMRI sample (n=68). The overlayed functional brain image shows the main effect of 2-back task-related activation in *AKT1* rs1130233 minor allele carriers vs major allele homozygotes at the ventral prefrontal cortex ($p<0.005$ uncorrected for display only). The graph shows the corresponding extracted parameter estimates representing task-related activation according to *COMT* and *AKT1* genotype. There was an *AKT1*-by-*COMT* interaction at $p<0.05$ (see Results) where combined deleterious *COMT* Val homozygotes and *AKT1* A-carriers had disproportionately inefficient activation.



Supplementary Figure S3: Plots of extracted neuroimaging parameter estimates showing *COMT*-by-*AKT1* interactions. Filled circles and solid lines represent *AKT1* rs1130233 A-carriers; unfilled circles and dashed lines represent *AKT1* G-homozygotes. (A): Extracted fMRI parameter estimates representing task-related prefrontal cortex activation during 2-back from the first fMRI dataset. (B) and (C): Extracted fMRI parameter estimates representing task-related prefrontal cortex activation from the second fMRI dataset. In both fMRI datasets, there were significant *COMT*-by-*AKT1* interactions ($p<0.05$, see

Results) where combined deleterious *COMT* Val homozygotes and *AKT1* A-carriers engaged disproportionately increased activation. (D): Extracted volume parameter estimates from the structural neuroimaging dataset. There was a significant *COMT*-by-*AKT1* interaction ($p<0.005$, see Results) where combined deleterious *COMT* Val homozygotes and *AKT1* A-carriers had reduced gray matter volume.

Supplementary References:

1. Emamian, E.S., Hall, D., Birnbaum, M.J., Karayiorgou, M., and Gogos, J.A. 2004. Convergent evidence for impaired AKT1-GSK3 beta signaling in schizophrenia. *Nat. Genet.* 36:131-137.
2. Schwab, S.G., Hoefgen, B., Hanses, C., Hassenbach, M.B., Albus, M., Lerer, B., Trixler, M., Maier, W., and Wildenauer, D.B. 2005. Further Evidence for Association of Variants in the AKT1 Gene with Schizophrenia in a Sample of European Sib-Pair Families. *Biol. Psychiatry* 58:446.
3. Luna, A., and Nicodemus, K.K. 2007. snp.plotter: an R based SNP/haplotype association and linkage disequilibrium plotting package. *Bioinformatics* 23:774-776.