

Supplementary Online Content

Koo M-S, Levitt JJ, Salisbury DF, Nakamura M, Shenton ME, McCarley RW. A cross-sectional and longitudinal magnetic resonance imaging study of cingulate gyrus gray matter volume abnormalities in first-episode schizophrenia and first-episode affective psychosis. *Arch Gen Psychiatry*. 2008;65(7):746-760.

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eTable 1. Percentages of Change of Cingulate Gyrus Gray Matter Volume in Patients Subgrouped by Medication Type, Compared with HCs

Change, % (SED) ^a	FESZ Group (n=17)		FEAFF Group (n=18)		HC Group (n=18)	Overall Group Comparison of Percentage of Changes (1-Factor ANOVA by group) ^b		Post Hoc Tukey HSD Test
	+TYP (n = 8) ^c	+ATYP (n = 9) ^c	+MS (n = 10) ^d	-MS (n = 8) ^d		F _{6,48}	P Value	
Anterior cingulate								
Left	-6.06 (1.26)	-4.61 (1.34)	-2.91 (0.93)	-2.48 (0.49)	-0.38 (0.43)	7.31	<.001	FESZ + TYP = FESZ + ATYP < HC; FEAFF + MS = FEAFF - MS = HC ^{e,f}
Right	-6.98 (1.04)	-4.98 (1.26)	-1.59 (1.36)	-2.25 (0.77)	-0.46 (0.47)	8.05	<.001	FESZ + TYP = FESZ + ATYP < HC; FEAFF + MS = FEAFF - MS = HC ^{g,h}
Posterior cingulate								
Left	-1.24 (1.31)	-2.59 (0.77)	0.31 (0.54)	-1.34 (1.06)	-0.24 (0.39)	2.46	.06	FESZ + TYP = FESZ + ATYP = HC; FEAFF + MS = FEAFF - MS = HC ^{i,j}
Right	-1.59 (0.93)	-2.46 (0.86)	-0.98 (0.85)	-0.39 (1.17)	-0.35 (0.31)	1.43	.24	FESZ + TYP = FESZ + ATYP = HC; FEAFF + MS = FEAFF - MS = HC ^{k,l}

Abbreviations: +ATY, with atypical neuroleptic treatment without exposure to typical neuroleptics at times 1 and 2 magnetic resonance imaging (MRI); FEAFF, first-episode affective psychosis; FESZ, first-episode schizophrenia; HCs, healthy comparison subjects; +/-MS, with/without mood stabilizer treatment; SED, standard error of the difference; +TYP, with typical neuroleptic treatment.

^aCalculated as (volume at second MRI - volume at baseline MRI)/(volume at baseline MRI × 100).

^bCalculated using 1-way analysis of variance (ANOVA) by group for the percentages of change of cingulate gyrus gray matter relative volumes in each region. The groups include the 5 given in the Table (FESZ + TYP, FESZ + ATYP, FEAFF + MS, FEAFF - MS, and HC).

^cTypical neuroleptics include perphenazine in 6 patients and haloperidol in 2; atypical neuroleptics, olanzapine in 5 patients, risperidone in 2, clozapine in 1, and quetiapine in 1.

^dIncludes lithium or valproic acid. The FEAFF - MS group includes 2 patients who were prescribed mood stabilizers but did not adhere to the treatment.

^eP = .82 between the FESZ + TYP and FESZ + ATYP groups, P = .001 between the FESZ + TYP and HC groups, and P = .004 between the FESZ + ATYP and HC groups.

^fP = .90 between the FEAFF + MS and FEAFF - MS groups, P = .12 between the FEAFF + MS and HC groups, and P = .06 between the FEAFF - MS and HC groups.

^gP = .65 between the FESZ + TYP and FESZ + ATYP, P < .001 between the FESZ + TYP and HC groups, and P = .005 between the FESZ + ATYP and HC groups.

^hP = .88 between the FEAFF + MS and FEAFF - MS groups, P = .58 between the FEAFF + MS and HC groups, and P = .32 between the FEAFF - MS and HC groups.

ⁱP = .76 between the FESZ + TYP and FESZ + ATYP groups, P = .85 between the FESZ + TYP and HC groups, and P = .11 between the FESZ + ATYP and HC groups.

^j $P = .61$ between the FEAFF + MS and FEAFF – MS groups, $P = .97$ between the FEAFF + MS and HC groups, and $P = .85$ between the FEAFF – MS and HC groups.

^k $P = .94$ between FESZ + TYP and FESZ + ATYP groups, $P = .73$ between the FESZ + TYP and HC groups, and $P = .20$ between the FESZ + ATYP and HC groups.

^l $P = .88$ between the FEAFF + MS and FEAFF – MS groups, $P > .99$ between the FEAFF + MS and HC groups, and $P > .99$ between the FEAFF – MS and HC groups.

eTable 2. Correlations Between Anterior Cingulate Gyrus Percentage of Volume Changes and BPRS Symptom Changes Over Time

BPRS	ρ (P Value)			
	FESZ Group (n = 17)		FEAFF Group (n = 18)	
	Withdrawal Factor	Anxiety- Depression Factor	Withdrawal Factor	Anxiety- Depression Factor
Subgenual cingulate				
Left	-0.10 (.71)	-0.35 (.14)	-0.44 (.07)	-0.32 (.22)
Right	-0.11 (.69)	-0.21 (.46)	-0.14 (.59)	0.19 (.46)
Affective cingulate				
Left	-0.24 (.38)	-0.22 (.44)	0.26 (.16)	0.08 (.77)
Right	-0.60 (.02) ^a	-0.05 (.87)	-0.22 (.40)	-0.28 (.29)
Cognitive cingulate				
Left	-0.25 (.38)	-0.16 (.57)	-0.08 (.76)	0.02 (.93)
Right	-0.50 (.06)	-0.09 (.75)	-0.11 (.68)	0.33 (.20)
Posterior cingulate				
Left	-0.39 (.15)	0.07 (.82)	0.12 (.65)	-0.15 (.57)
Right	-0.35 (.20)	0.38 (.11)	-0.04 (.87)	-0.15 (.34)

Abbreviations: BPRS, Brief Psychiatric Rating Scale; FEAFF, first-episode affective psychosis; FESZ, first-episode schizophrenia.

^a $P < .05$.

eTable 3. Analysis of the Medication Good-Responder Patient Subgroups vs the Poor-Responder Subgroups in FESZ and FEAFF Groups^a

Mean Changes, % (SED) ^b	FESZ Group (n = 17)			FEAFF Group (n = 18)		
	Good-Responder Subgroup (n=9)	Poor-Responder Subgroup (n=8)	z score (2-Tailed P Value) ^c	Good-Responder Subgroup (n=12)	Poor-Responder Subgroup (n=6)	z Score (2-Tailed P Value) ^c
Subgenual cingulate	-3.85 (1.04)	-4.62 (1.55)	-0.5 (.63)	-5.22 (1.17)	-6.22 (1.57)	-0.3 (.78)
Left	-2.63 (1.39)	-4.36 (1.81)	-0.5 (.63)	-4.14 (1.03)	-8.70 (0.76)	-2.6 (.009) ^d
Right	-4.66 (1.18)	-4.49 (1.83)	-0.5 (.63)	-4.81 (1.46)	-6.22 (2.22)	-0.7 (.51)
Affective cingulate	-3.74 (0.64)	-8.82 (0.99)	-3.2 (.001) ^e	-2.04 (0.97)	-2.57 (0.70)	-0.8 (.40)
Left	-4.81 (1.42)	-7.58 (0.76)	-1.2 (.25)	-3.65 (1.39)	-2.33 (1.02)	-0.4 (.71)
Right	-2.80 (1.46)	-10.36 (4.74)	-3.4 (.001) ^e	-0.67 (1.28)	-2.84 (0.98)	-1.2 (.22)
Cognitive cingulate	-3.94 (1.54)	-6.05 (1.15)	-1.0 (.34)	-1.87 (0.74)	-0.38 (1.25)	-1.3 (.19)
Left	-2.56 (1.37)	-5.80 (2.13)	-1.2 (.258)	-1.24 (0.93)	-1.54 (1.04)	-0.2 (.85)
Right	-5.12 (1.97)	-5.54 (1.74)	-0.3 (.77)	-2.70 (1.38)	-0.17 (1.83)	-0.9 (.35)
Posterior cingulate	-2.42 (0.55)	-1.47 (1.05)	-0.3 (.773)	-0.33 (0.56)	-0.92 (0.82)	-0.6 (.57)
Left	-2.47 (0.70)	-1.37 (1.37)	-0.5 (.63)	-0.36 (0.59)	-1.42 (0.89)	-1.4 (.16)
Right	-2.44 (0.85)	-1.62 (0.94)	-0.8 (.44)	-0.99 (0.89)	-0.36 (1.02)	-0.7 (.51)

Abbreviations: FEAFF, first-episode affective psychosis; FESZ, first-episode schizophrenia; SED, standard error of the difference.

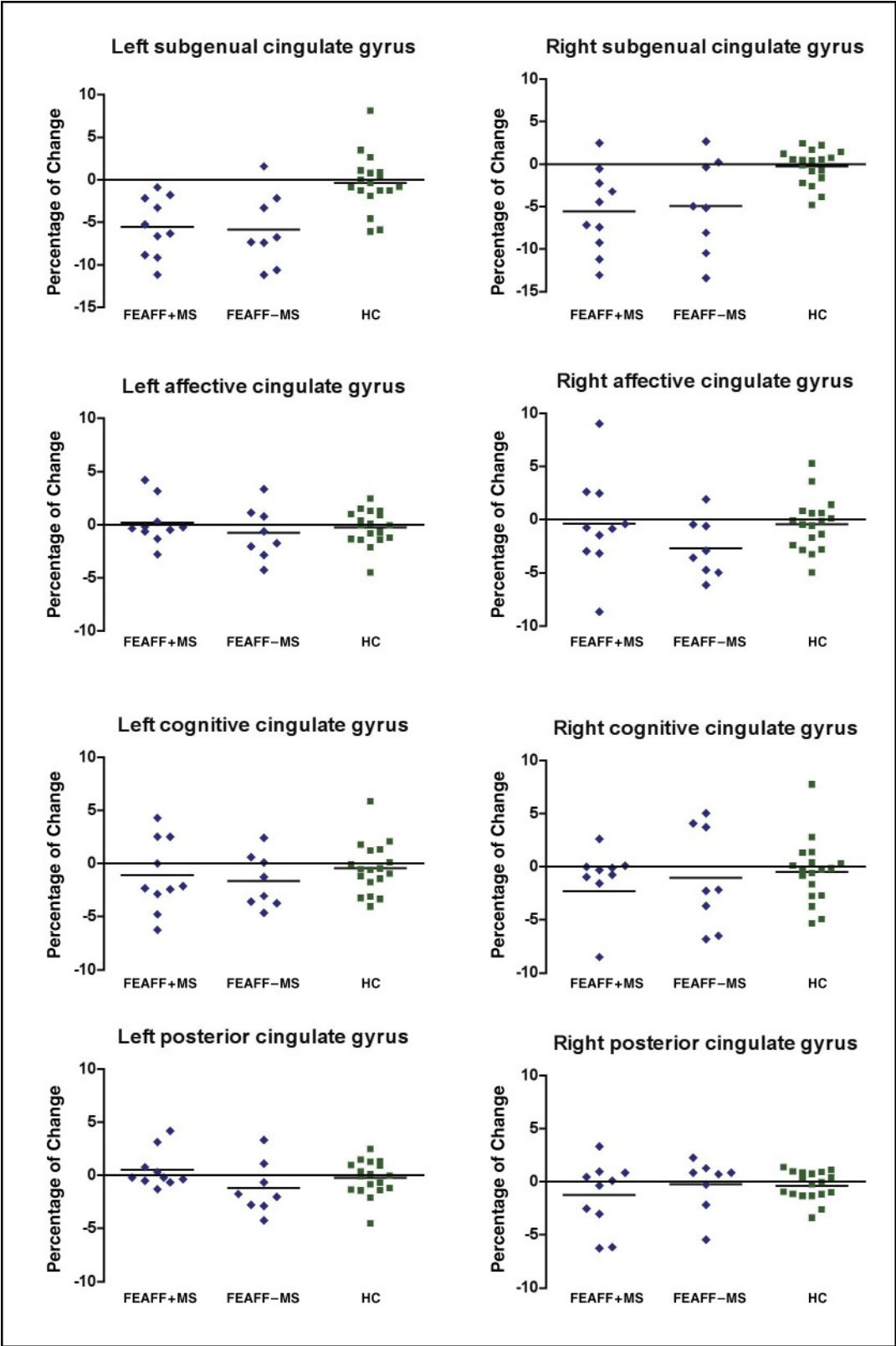
^aThe good-responder subgroup had Brief Psychiatric Rating Scale (BPRS) scores that decreased more than 20 points (20 was derived from a median value to divide the group into 2 similarly sized subgroups); the poor-responder subgroup, BPRS scores that decreased less than 20 points, did not change, or increased.

^bCalculated as (volume at second image - volume at baseline image)/(volume at baseline image × 100).

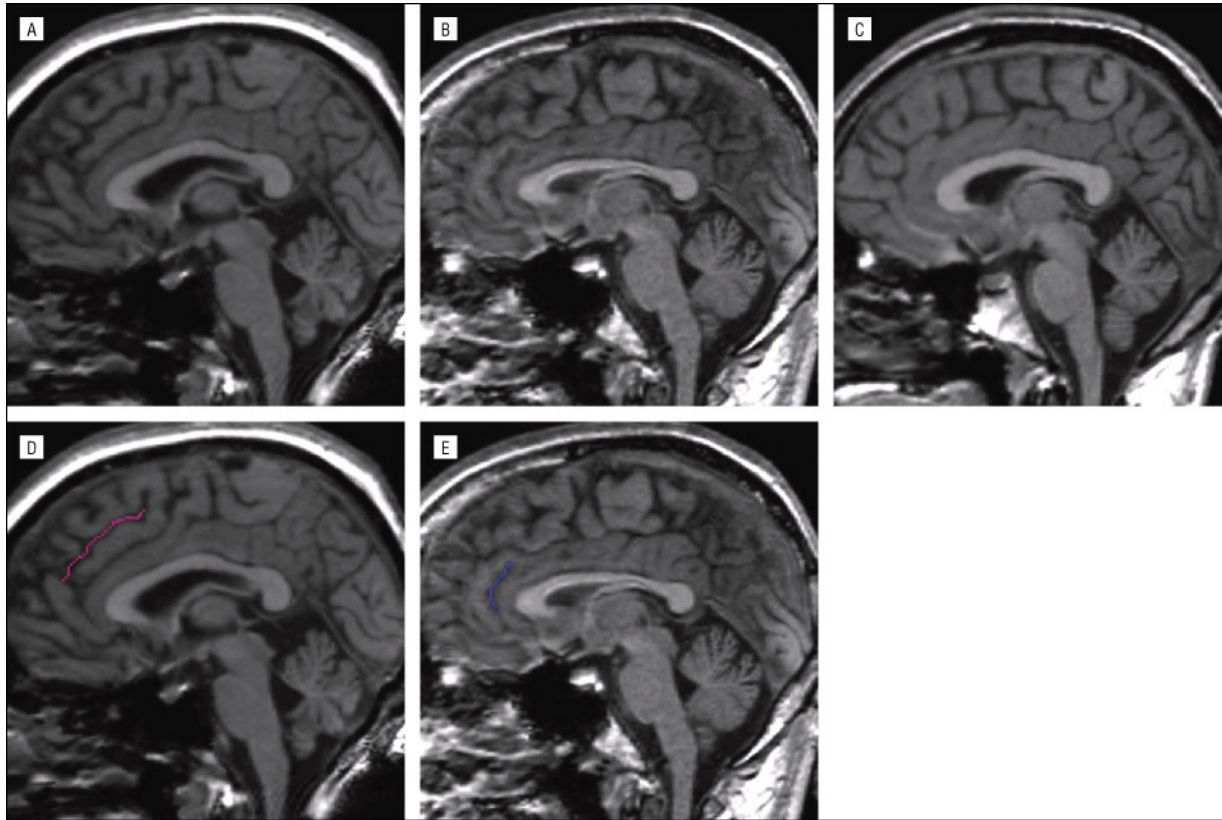
^cThe z score was derived from nonparametric Mann-Whitney tests comparing both patient groups because individual groups (n < 13) did not show a normal distribution.

^dDifference was significant ($P < .05$); however, not significant when applied with Bonferroni correction (0.05/8).

^eDifference was significant ($P < .05$); also significant when applied with Bonferroni correction (0.05/8).



eFigure 1. Percentages of change in 1½ years in relative volumes of the left and right cingulate gyrus gray matter in patients with first-episode affective psychosis (FEAFF) (n=18) receiving (+MS) and not receiving mood stabilizers (–MS) (consisting of lithium carbonate and/or valproic acid) and in healthy comparison subjects (HCs) (n=18). The FEAFF – MS group included 2 patients who were prescribed mood stabilizers but did not adhere to treatment. Percentage of change is calculated as (volume at second image – volume at baseline image)/(volume at baseline image × 100). Horizontal line indicates mean. Repeated-measures analysis of variance (ANOVA) of relative volume difference (percentage of change) with group (FEAFF + MS, FEAFF – MS, or HC) as the between-subjects factor and hemisphere (left vs right) and region (subgenual, affective, cognitive, or posterior) as the within-subjects factors revealed a significant main effect for group ($F_{2,33} = 11.11$; $P < .001$) and region ($F_{3,99} = 11.35$; $P < .001$). There was a significant interaction between region and group ($F_{6,99} = 3.80$; $P = .002$). There was no significant effect for hemisphere ($F_{1,33} = 0.26$; $P = .62$), and there were no significant interactions of hemisphere × group ($F_{2,33} = 0.15$; $P = .86$), region × hemisphere ($F_{3,99} = 0.22$; $P = .81$), and region × hemisphere × group ($F_{6,99} = 1.31$; $P = .26$). Follow-up 1-way ANOVA revealed significant differences only in the left ($F_{2,33} = 9.77$; $P < .001$) and right ($F_{2,33} = 7.45$; $P = .002$) subgenual relative volume percentages of change. Post hoc Tukey Honestly Significant Difference (HSD) tests indicated that the left ($P = .003$) and right ($P = .004$) subgenual cingulate volumes percentages of change of FEAFF + MS patients were significantly bigger than those of the HCs, which were not significantly different from those of the FEAFF – MS patients. Also, left ($P = .003$) and right ($P = .004$) subgenual cingulate volumes percentages of change of FEAFF – MS patients were significantly bigger than those of the HCs. Additional repeated-measures ANOVA of relative volume difference (percentage of change) with group (affective psychosis treated with lithium, affective psychosis without lithium treatment, and healthy comparison) as the between-subjects factor and hemisphere (left vs right) and region (subgenual, affective, cognitive, or posterior) as the within-subjects factors revealed a significant main effect for group ($F_{2,33} = 11.48$; $P < .001$) and region ($F_{3,99} = 7.18$; $P < .001$). There was a significant interaction between region and group ($F_{6,99} = 4.99$; $P < .001$). There was no significant effect for hemisphere ($F_{1,33} = 0.15$; $P = .70$), and there were no significant interactions of hemisphere × group ($F_{2,33} = 2.20$; $P = .13$), region × hemisphere ($F_{3,99} = 1.30$; $P = .28$), and region × hemisphere × group ($F_{6,99} = 0.45$; $P = .84$). Follow-up 1-way ANOVA revealed significant differences only in the left ($F_{2,33} = 11.41$; $P < .001$) and right ($F_{2,33} = 7.55$; $P = .002$) subgenual relative volume percentage of changes. Post hoc Tukey HSD tests indicated that the left ($P = .04$) and right ($P = .03$) subgenual cingulate volumes percentage of changes of the FEAFF + lithium patients were significantly bigger than those of the HCs, which were not significantly different from those of the FEAFF – lithium patients (left, $P = .33$; right, $P = .87$). In addition, the left ($P = .001$) and right ($P = .002$) subgenual cingulate volumes percentage of changes of FEAFF – lithium patients were significantly bigger than those of HCs.



eFigure 2. Paracingulate sulcus (PCS) pattern. The magnetic resonance images of the PCS show the distinct PCS patterns evaluated in this study. A through C, The PCS is prominent (A), present (B), and absent (C). D and E, lines have been drawn on upper panel images (A and B, respectively) to indicate the prominent PCS (red line) (D) and a present PCS (blue line) (E).

Supplemental Text

The magnetic resonance imaging (MRI) protocol used 2 pulse sequences on a 1.5-T MRI system (GE Medical Systems, Milwaukee, Wisconsin). Briefly, a 3-dimensional Fourier-transformed spoiled gradient-recalled (SPGR) acquisition sequence yielded contiguous coronal SPGR images (echo time, 5 ms; repetition time, 35 ms; 1 repetition; nutation angle, 45°; field of view, 24 cm; acquisition matrix, $256 \times 256 \times 124$; voxel dimension, $0.9375 \times 0.9375 \times 1.5$ mm). Next, a double-echo spin-echo yielded contiguous axial (54 proton-density-weighted and 54 T2-weighted) sections (slices) throughout the brain (echo times, 30 and 80 ms; repetition time, 3000 ms; field of view, 24 cm; an interleaved acquisition with 3-mm section thickness; voxel dimensions, $0.9375 \times 0.9375 \times 3.0$ mm). Images were realigned using the anterior commissure/posterior commissure line and the sagittal sulcus to correct head tilt and resampled into isotropic voxels (0.9375 mm^3).