META-ANALYSIS

Meta-analysis of 41 Functional Neuroimaging Studies of Executive Function in Schizophrenia

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Context: Prefrontal cortical dysfunction is frequently reported in schizophrenia. It remains unclear whether this represents the coincidence of several prefrontal region- and process-specific impairments or a more unitary dysfunction in a superordinate cognitive control network. Whether these impairments are properly considered reflective of hypofrontality vs hyperfrontality remains unresolved.

Objectives: To test whether common nodes of the cognitive control network exhibit altered activity across functional neuroimaging studies of executive cognition in schizophrenia and to evaluate the direction of these effects.

Data Sources: PubMed database.

Study Selection: Forty-one English-language, peer-reviewed articles published prior to February 2007 were included. All reports used functional neuroimaging during executive function performance by adult patients with schizophrenia and reported whole-brain analyses in standard stereotactic space. Tasks primarily included the delayed match-to-sample, N-back, AX-CPT, and Stroop tasks.

Data Extraction: Activation likelihood estimation modeling reported activation maxima as the center of a 3-dimensional gaussian function in the meta-analysis, with statistical thresholding and correction for multiple comparisons.

Data Synthesis: In within-group analyses, healthy controls and patients activated a similarly distributed cortical-subcortical network, prominently including the dorsolateral prefrontal cortex (PFC), ventrolateral PFC, anterior cingulate cortex (ACC), and thalamus. In between-group analyses, patients showed reduced activation in the left dorsolateral PFC, rostral/dorsal ACC, left thalamus (with significant co-occurrence of these areas), and inferior/posterior cortical areas. Increased activation was observed in several midline cortical areas. Activation within groups varied modestly by task.

Conclusions: Healthy adults and schizophrenic patients activate a qualitatively similar neural network during executive task performance, consistent with the engagement of a general-purpose cognitive control network, with critical nodes in the dorsolateral PFC and ACC. Nevertheless, patients with schizophrenia show altered activity with deficits in the dorsolateral PFC, ACC, and mediodorsal nucleus of the thalamus. Increases in activity are evident in other PFC areas, which could be compensatory in nature.

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Impaired cognition is a core, disabling feature of schizophrenia, with no established treatment. Although numerous deficits have been described across perceptual, attentional, mnemonic, linguistic, and intellectual functions, impaired executive functions are among the most widely observed, and they are consistently associated with impaired function of the prefrontal cortex (PFC).[1] Different aspects of executive dysfunction have been examined, including multiple facets of working memory, response inhibition, conflict processing, and problem solving, demonstrating deficits across a range of circumscribed PFC regions, such as the ventrolateral PFC (VLPFC), dorsolateral PFC (DLPFC), ventromedial PFC, and anterior cingulate cortex (ACC). A recent quantitative meta-analysis of 12 N-back studies found alterations among schizophrenic subjects compared with healthy controls in several nodes of this neural network, including reduced activity in the DLPFC and increased activity in the VLPFC , ACC, and left frontal pole.[2] Other studies have reported reduced activity in the VLPFC during other working memory tasks[3] and in the ACC during conflict processing.[4,5]

One possible interpretation of these findings is that there is a general deficit in PFC function in schizophrenia, with find-

ings in a given task reflecting a distinct underlying circuitry that supports each particular function, eg, the VLPFC for working memory maintenance, the DLPFC for working memory manipulation or interference control, and the frontopolar cortex for response inhibition. Alternatively, there could be a set of regions that show impaired function in schizophrenia across a range of tasks and other areas with preserved or compensatory function. One hypothesis suggests that there is impaired DLPFC activity in the presence of an intact VLPFC.[6] Together with reports of selective loss of neuropil in dorsal vs ventral regions of the PFC, this hypothesis might imply some subregion specificity to frontal dysfunction, ie, the DLPFC is impaired while the VLPFC is not. An influential model of PFC function assigns the dorsolateral regions a critical superordinate role in regulating cognitive control.[7] According to this model, the DLPFC maintains the context or task set to ensure accurate and flexible performance during higher-level cognition, while medial frontal regions (eg, the ACC) support dynamic adjustments in control in concert with the DLPFC.[8,9] According to this view, dysfunction in general-purpose, high-level cognitive control functions of the dorsolateral and medial PFC could result in a wide range of deficits in different executive functions in schizophrenia.

In this article, we use meta-analysis to test whether the various executive function deficits observed across functional neuroimaging studies in schizophrenia represent the coincidence of several PFC subregion- and task-specific dysfunctions or a more unitary dysfunction of a general-purpose, DLPFC/ACC-based cognitive control network. In this context, the meta-analytic approach is uniquely valuable, as it allows us to test a research problem that is not easily addressed in a single study; to overcome equivocation or inconsistencies in an existing literature; and to provide the reader with the landscape of a research domain, which in contemporary biomedical research may be more highly valued than the results of an individual study.[10] Activation likelihood estimation (ALE) is a meta-analytic tool that models 3-dimensional coordinates (from reported activations in a standard space) as the center of a 3-dimensional gaussian distribution.[11] This obviates the need for raw data and thus increases the potential set of studies subject to meta-analysis and whole-brain analyses corrected for multiple comparisons.[11] Activation likelihood estimation has been implemented to address a variety of research questions in both healthy subjects and clinical samples.[12]

We used ALE to test the largest sample to date of studies of PFC-dependent executive cognition in schizophrenia. We hypothesized that, across a range of discrete PFC-dependent executive tasks, schizophrenic patients would show a deficit in a general-purpose DLPFC/ACC control/conflict-processing system. In contrast, if schizophrenia is the expression of multiple "hits" against a number of distinct component executive functions, it would be difficult to detect robust between-group differences when these varied executive function studies are integrated in a single analysis. Relatively distinct task-dependent patterns of activation should be observed within tests of these functions and not across different executive functions.

METHODS

STUDY SELECTION

A PubMed literature search was performed to identify English-language, peer-reviewed studies that investigated executive function in schizophrenic patients and healthy control subjects using functional magnetic resonance imaging or positron emission tomography. Executive functions can be defined as processes necessary to control or regulate other cognitive processes in the service of goal-directed behavior. The term *cognitive control* is often used to describe executive functions to emphasize the regulatory component of this aspect of information processing. For this analysis, we searched for studies that used task paradigms that are typically associated with executive functions or cognitive control. These included delayed match-to-sample or delayed response (including Sternberg item recognition), go/no-go (including AX-CPT), mental arithmetic, N-back, oddball, sequence recall, Stroop, Wisconsin Card Sort, and word generation tasks. Studies that did not report results as 3-dimensional coordinates in standard stereotactic space or that reported only data from individual subjects or deactivations were excluded. Forty-one studies published prior to February 2007 met these criteria (**Table 1**).[3,5,13-51] Study design features are indicated in Table 1, including clinical characteristics like illness duration and symptom severity; sex ratio among the patient group; medication status; block vs event-related design; and performance-matched vs nonmatched groups for analysis. From this group of studies, coordinate results of within-group activations and between-group differences were divided into 4 groups: activations in schizophrenic patients, activations in normal control subjects, increases in schizophrenic patients relative to controls, and increases in controls relative to schizophrenic patients. To evaluate potential task-specific patterns of activation, we also repeated the within-group analyses in an identical manner but with the subsets of studies segregated by task type.

ACTIVATION LIKELIHOOD ESTIMATION

Activation likelihood estimation meta-analysis was conducted.[11,52] All data processing was performed in the BrainMap environment.[53,54] On insertion into the database, the spatial normalization template of each article was noted and the coordinates were automatically transformed to allow analysis relative to a single template.[55] Coordinates were converted using the icbm2tal transformation,[56] which has shown to provide improved fit over the mni2tal transformation.[57] Included foci were smoothed with a full-width at half-maximum of 12 mm, and the ALE statistic was computed for every voxel in the brain. Separate ALE maps were created for each of the 4 types of statistical comparisons. Statistical significance was determined using a permutation test of randomly generated foci, corrected for multiple comparisons. Five thousand permutations were computed using the same full-width at half-maximum value and the same number of foci used in computing ALE values. The final ALE maps were thresholded at $P < .05$ (false discovery rate–corrected) with an extent threshold greater than 400 mm^3 and overlaid onto a template generated by spatially normalizing the International Consortium for Brain Mapping template to Talairach space.[58]

FRACTIONAL SIMILARITY NETWORK ANALYSIS

To expand on our basic meta-analysis and to determine if specific brain regions co-occur frequently across studies, fractional similarity network analysis was used.[59] Fractional similarity network analysis identifies subordinate networks within

Table 1. Published Studies Included in the ALE Meta-analysis of Executive Function by Task

Source	Contrasts	Sample Size, No.		Mean, y		Patient Medication	Mean Symptom Scores	Block Design	Performance Matched	PFC in SCZ[a]
		SCZ (Male Patients)	CON	Age	Duration of Illness					
Delayed Match to Sample										
Crespo-Facorro et al,[13] 2001	SCZ, CON, SCZ>CON, CON>SCZ	19 (14)	34	29.6		8 Naive; 11 free for 3 weeks	SANS/SAPS item score, negative, 2.53; positive, 2.55; disorganized, 1.26	Yes	No	↓
Manoach et al,[14] 2000	CON, SCZ	9 (7)	9	42.4	25.0	1 Atypical; 7 typical	PANSS, positive, 14.4; negative, 21.6; BPRS total, 20.1	Yes	Both matched and unmatched	↑/–
Manoach et al,[15] 2005	SCZ, SCZ>CON, CON>SCZ	19 (14)	12	42	18	9 Atypical; 2 typical; 2 both; 2 none	PANSS, positive, 13; negative, 14; BPRS total, 16; SANS total, 26	Yes	No	↓↑
Quintana et al,[16] 2003	SCZ, CON	8 (6)	8	29.3	8.5	All atypical	NA	Yes	No	↓↑ (ROI/ANOVA)
Tan et al, 2005[17]	SCZ>CON, CON>SCZ	11 (5)	11	25.0	0.2[b]	5 Olanzapine; 6 risperidone	PANSS, positive, 10.2; negative, 17.5; general, 28.4	Yes	SCZ=CON[c]	↓↑
Go/No-Go										
Carter et al,[18] 2001	CON>SCZ	17 (12)	18	33.5	16.0	6 Typical; 11 atypical	PANSS, total, 25.7; positive, 7.1; negative, 10.7	No	No	↓
Laurens et al,[19] 2003	SCZ>CON	10 (12)	16	32.9	11	All atypical	SSPI total, 8.3; positive, 2.0; negative, 1.0; disorganized, 0.9	No	No	↓↑
MacDonald and Carter,[20] 2003	SCZ, CON	17 (12)	17	34.2		11 Atypical; 6 typical	PANSS, positive, 7.1; negative, 10.7; disorganized, 7.9	No	No	↓ (ROI/ANOVA)
MacDonald et al,[21] 2005	SCZ, CON, CON>SCZ	18 (12)	28	27.5[b]		All naive	SAPS/SANS, positive, 15.7; negative, 7.3; disorganized, 7.3	No	No	↓↑
Rubia et al,[22] 2001	SCZ>CON, CON>SCZ	6 (6)	7	40	15.7	All taking medications	NA	Yes	SCZ=CON[c]	↓
Mental Arithmetic										
Hugdahl et al,[23] 2004	SCZ, CON, SCZ>CON, CON>SCZ	12 (6)	12	32.4	8.7	All taking medications	PANSS total, 58.2; BPRS total, 45.2	Yes	No	↓↑
N-Back										
Callicott et al,[24] 2000	SCZ>CON, CON>SCZ	13 (10)	18	33.0	10	NA	PSAS, 15.4	Yes	Both matched and unmatched	↓↑/↓↑
Callicott et al,[25] 2003	SCZ>CON, CON>SCZ	14 (11)	14	31.5		Mean 476 CPZ	NA	Yes	Both matched and unmatched	↓/↓↑
Honey et al,[26] 1999	SCZ, CON	20 (20)	10	37.2	12.9	Mean 194.5 CPZ	PANSS, positive 8.4; negative 10.7; general, 20.2	Yes	SCZ=CON[c]	NA
Honey et al,[27] 2002	SCZ, CON	20 (20)	20	34.6	11.8	Mean 299 CPZ	PANSS, positive, 10.2; negative, 15.0; general, 26.9	Yes	SCZ=CON[c]	NA
Honey et al,[28] 2003	SCZ, CON, CON>SCZ	30 (27)	27	36.9	13	Mean 327.3 CPZ	PANSS, positive, 11.7; negative, 14.6; general, 26.3	Yes	No	↓
Jacobsen et al,[29] 2004	SCZ>CON	13 (9)	13	42.9		11 Atypical; 1 typical; 1 both	NA	Yes	No	↑
Jansma et al,[30] 2004	SCZ>CON	10 (8)	10	27.2		8 Clozapine; 2 olanzapine	PANSS, positive, 13.9; negative, 15.4; general, 31.0	Yes	No	↑
Kim et al,[31] 2003	SCZ, CON	12 (6)	12	26.2	2.8	All atypical	PANSS, positive, 14.1; negative, 17.6; general, 31.3	Yes	SCZ=CON[c]	NA
Meisenzahl et al,[32] 2006	CON, CON>SCZ	12 (11)	12	33.6		9 Naive; 3 postwashout	PANSS total, 54.6; SANS total, 63.9; BPRS total, 56.6	Yes	No	↓
Mendrek et al,[33] 2004	SCZ, CON, CON>SCZ	8 (6)	8	30		All atypical	SSPI total, 19.85	Yes	No	↓↑
Mendrek et al,[34] 2005	SCZ, CON, SCZ>CON	12 (9)	12	28.8		All atypical	SSPI total, 8.58	Yes	No	↓↑
Meyer-Lindenberg et al,[35] 2001	SCZ>CON, CON>SCZ	13 (10)	13	32.5		Postwashout for 2 weeks	NA	Yes	Both matched and unmatched	↓↑/↓↑
Sabri et al,[36] 2003	SCZ>CON	12 (7)	10	30.6		All taking medication	NA	Yes	SCZ=CON[c]	↑

(continued)

Table 1. Published Studies Included in the ALE Meta-analysis of Executive Function by Task (continued)

Source	Contrasts	Sample Size, No.		Mean, y		Patient Medication	Mean Symptom Scores	Block Design	Performance Matched	PFC in SCZ[a]
		SCZ (Male Patients)	CON	Age	Duration of Illness					
N-Back										
Salgado-Pineda et al,[37] 2004	CON>SCZ	14 (7)	14	25.1		All risperidone	SAPS total, 9.8; SANS total, 21.2	Yes	No	↓
Schneider et al,[38] 2007	SCZ>CON, CON>SCZ	48 (26)	57	31.0	1.9[b]	Mean 66-day treatment history; medications NA	PANSS, positive, 9.2; negative, 13.5; general, 25.3	Yes	No	↑
Tan et al,[39] 2006	SCZ>CON	15 (12)	26	32.7		Mean 501 CPZ	PANSS, positive, 11.6; negative, 16.6; general, 25.8	Yes	Both matched and unmatched	↑/↑
Walter et al,[40] 2003	SCZ>CON	15 (8)	15	28.7	5.5	13 Atypical; 1 typical; 1 none	PANSS, positive, 23.8; negative, 19.4; BPRS total, 53.9	Yes	Both matched and unmatched	↑/↑
Wykes et al,[41] 2002	SCZ>CON	6 (6)	6	35	>67%>10	9 Typical (mean 643 CPZ), 3 atypical	NA	Yes	No	↓
Yoo et al,[42] 2005	SCZ, CON, SCZ>CON, CON>SCZ	10 (8)	10	24.9	2.4	All atypical	BPRS total, 24.7	Yes	No	↓↑
Oddball										
Heckers et al,[43] 2004	SCZ, CON	19 (NA)	15	46.6		NA	PANSS, 64.6; SANS total, 38.5	Yes	SCZ=CON[c]	NA
Laurens et al,[44] 2005	SCZ, CON, CON>SCZ	29 (20)	28	31.6	7	27 Atypical; 1 typical; 1 no medication	SSPI total, 12.7; positive, 2.8; negative, 4.0; disorganized, 1.6	No	No	↓
Sequence Recall										
Stevens et al,[3] 1998	SCZ, CON	12 (8)	10	39.6		All taking medication	PANSS, positive, 16.1; negative, 17.2; general, 32.1	Yes	SCZ=CON[c]	↓ (ANOVA)
Johnson et al,[45] 2006	CON, SCZ>CON, CON>SCZ	18 (16)	18	36.9		All taking medication	NA	Yes	Both matched and unmatched	↓/↓↑
Stroop										
Seok Jeong et al,[46] 2005	SCZ, CON	10 (3)	10	29.2	4.3	7 Olanzapine; 6 risperidone	PANSS, positive, 13.2; negative, 15.9; general, 29.3	No	No	↓ (ANOVA)
Kerns et al,[5] 2005	SCZ, CON, SCZ>CON, CON>SCZ	13 (9)	13	35.6		2 Haloperidol; 11 atypical	PANSS total, 8.0; BPRS total, 28.1	No	No	↓
Weiss et al,[47] 2003	SCZ, CON, SCZ>CON, CON>SCZ	13 (13)	13	32.7	6.2	All atypical	PANSS, positive, 11.4; negative, 14.2; general, 23.3	Yes	SCZ=CON[c]	↓
Weiss et al,[48] 2007	SCZ, CON, SCZ>CON, CON>SCZ	8 (8)	8	29.5	2.4[d]	6 Naive; 2 taking medication	PANSS, positive, 20.0; negative, 17.0; general, 35.2	No	No	↓
Wisconsin Card Sorting										
Ragland et al,[49] 1998	SCZ, CON	15 (7)	15	33.5	11.1	6 Not taking medication; 9 with mean 631 CPZ	SAPS total, 27.2; SANS total, 29.8, BPRS total, 37.1	Yes	Both matched and unmatched	↓/↓
Word Generation										
Curtis et al,[50] 2001	SCZ, CON	5 (5)	5	29.6		NA	Total SANS subscale, negative, 23.2; positive, 20.8	Yes	No	↓
Weiss et al,[51] 2004	SCZ, CON	9 (9)	9	31.4		All atypical	PANSS, positive, 10.6; negative, 14.2; general, 23.5	Yes	SCZ=CON[c] (pre-scan)	No differences

Abbreviations: ALE, activation likelihood estimation; ANOVA, analysis of variance; BPRS, Brief Psychiatric Rating Scale; CON, control group; CON>SCZ, more activity in CON than SCZ; CPZ, chlorpromazine equivalents; NA, not available; PANSS, Positive and Negative Symptom Scale; PFC, prefrontal cortex; PSAS, Psychiatric Symptom Assessment Scale; ROI, region of interest; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SCZ, schizophrenia group; SCZ>CON, more activity in SCZ than CON; SSPI, Signs and Symptoms of Psychotic Illness; ↑, increased PFC neural activity in SCZ compared with CON; ↓, decreased PFC neural activity in SCZ compared with CON; ↓↑, both increased and decreased activity in PFC areas compared with CON; –, no change in PFC activity for SCZ compared with CON.

[a] Arrows separated by a slash indicate the direction of PFC effects as a function of performance matching (right) or not (left).

[b] All patients were having their first psychotic episode.

[c] Without performance matching.

[d] Six patients were having their first psychotic episode.

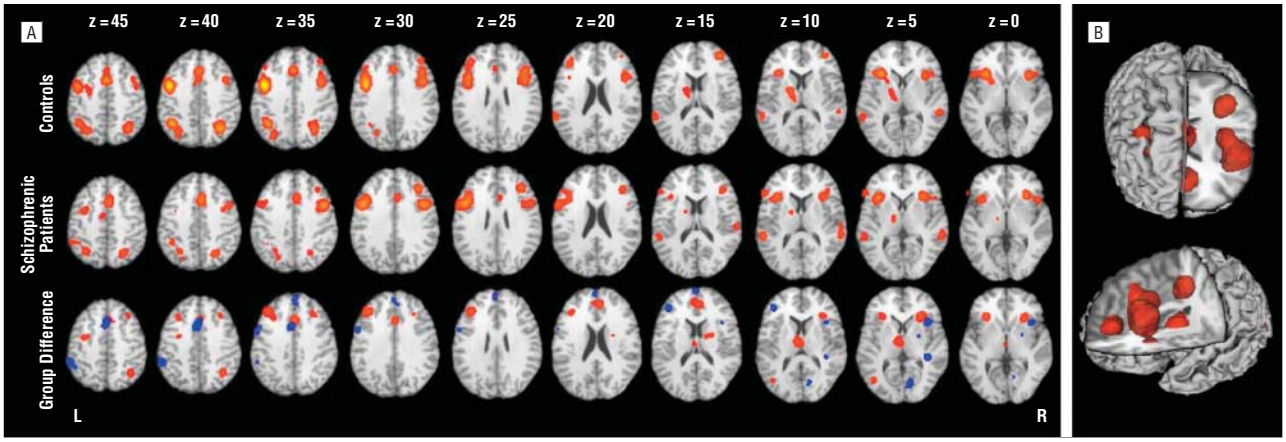

Figure 1. Global analysis of executive function studies in schizophrenia. A, Brain regions with significant activation across executive function task types. In the bottom row, clusters in which controls showed more activation than schizophrenic patients are in red and clusters in which schizophrenic patients showed more activation than controls are in blue. B, Three-dimensional rendering of areas with more activation in controls than in schizophrenic patients across task types (global). L indicates left; R, right.

a larger network by creating a co-occurrence matrix, in which each element indicates how often a given pair of regions is co-activated in a given study. This is accomplished with a general similarity coefficient, the fraction of 1-1 and 0-0 binary matches between 2 patterns. Using this coefficient, fractional similarity network analysis iteratively groups regions into subnetworks based on the likelihood that those regions co-occur across studies. A cluster threshold of 100 mm^3 was applied to ALE results prior to fractional similarity network analysis. No adjustment was made for varying significance thresholds across studies, as *P* values were highly variable in value; correction for multiple comparisons; or application at the voxel vs cluster level. As in all previously published ALE analyses, we chose to include all available articles (with statistically significant results) rather than exclude some on the basis of the statistical methods used. These were, however, conducted only on reports of whole-brain analyses. We used fractional similarity network analysis to evaluate whether, among those brain regions exhibiting significant activity changes in the patients relative to controls, some might co-occur together across the full (global) set of studies. This would suggest the presence of a deficit in a distinct subnetwork that mediates PFC-dependent cognitive processes.

RESULTS

GLOBAL ANALYSIS OF ALL STUDIES

Within-Group Analysis of Controls

In reporting these data, we emphasize functional brain regions (eg, DLPFC) to complement the tabulation of anatomic descriptions (eg, gyri or Brodmann areas). This analysis revealed robust activation of a broad cortical-subcortical network, including bilateral DLPFC (extending from the mid-DLPFC posteriorly into the dorsal premotor cortex); bilateral VLPFC (anterolateral areas and frontal opercular cortical areas, extending into subjacent insular cortex); and a large area centered on the dorsal ACC (extending superiorly into the supplementary motor area [SMA] and pre-SMA) (**Figure 1** and **Table 2**). More posterior neocortical areas were observed in the temporal and parietal lobes. Subcortical areas of activation notably included a large area that covered much of the left thalamus (centered on anterolateral nuclei but including the extent of the mediodorsal nucleus of the thalamus) and the left cerebellar declive.

Within-Group Analysis of Schizophrenic Patients

This analysis also revealed robust activation of a broad cortical-subcortical network, very similar in qualitative pattern to that of control subjects. This included areas of activation in the DLPFC, which was somewhat more restricted than that for the controls but also covered the mid-DLPFC, dorsal premotor cortex, and VLPFC, and a midline frontal cortical area extending from the dorsal ACC into the SMA. While the extent of activation in the ACC/SMA regions was roughly comparable between groups, the peak activation in the patients was displaced 8 mm posteriorly and inferiorly from that of the controls (Table 2). More posterior neocortical areas of activation were found in the temporal and parietal cortex; subcortical areas, including a left thalamus cluster that was considerably smaller than that found in controls; and the left cerebellar declive.

Between-Group Comparisons

In these direct comparisons, a number of the brain areas from the cortical-subcortical network described above were significantly reduced in patients relative to controls. These included the bilateral DLPFC, right VLPFC (extending from the right claustrum), right ventral premotor cortex, and 2 large midline frontal cortical areas, including the dorsal ACC and a more anterior and inferior area that peaked in the medial frontal gyrus but also extended into the adjacent ACC. Posterior neocortical areas were also observed in the parietal and occipital cortex. Subcortical areas included the right putamen and a large area in the left thalamus (prominently including the mediodorsal nucleus). This between-group analysis was repeated excluding the N-back studies (leaving 22 remaining studies). All differences in increases in controls relative to schizophrenic patients in the PFC remained significant except in the right

Table 2. Brain Regions Exhibiting Significant Activity Across the Full Set of Cognitive Tasks

Brain Region[a]	Volume, mm³	Brodmann Area	Talairach Coordinates, x, y, z
Healthy Controls			
Right superior frontal gyrus	400	9	40, 38, 32
Right middle frontal gyrus	1104	10	36, 44, 14
	688	6	32, −6, 54
Left superior frontal gyrus	5400	6	0, 8, 48
Left precentral gyrus	11584	6	−42, 2, 36
Right precentral gyrus	6720	9	42, 6, 32
Left superior temporal gyrus	1288	22	−58, −46, 18
Right middle temporal gyrus	512	22	56, −38, 6
Left inferior parietal lobule	4608	40	−38, −54, 38
Right precuneus	3120	19	32, −62, 40
Left claustrum	4496		−30, 18, 2
Right insula	2056		34, 16, 2
Left thalamus	1464		−14, −6, 10
Left cerebellum (declive)	1464		−38, −70, −14
Schizophrenic Patients			
Right middle frontal gyrus	5856	9	36, 32, 28
	4104	9	44, 8, 32
Left middle frontal gyrus	2472	6	−30, 0, 52
Left inferior frontal gyrus	9736	9	−44, 8, 28
Right cingulate gyrus	5800	32	4, 16, 40
Right superior temporal gyrus	1240	22	60, −36, 8
Left superior temporal gyrus	1048	22	−54, −40, 10
Right superior parietal lobule	1400	7	24, −64, 42
Left superior parietal lobule	1176	7	−30, −60, 44
Left inferior parietal lobule	592	40	−48, −48, 46
Left thalamus	464		−12, −12, 4
Left cerebellum (declive)	824		−36, −62, −16
Greater Activity in Controls Than Schizophrenic Patients			
Left middle frontal gyrus	3096	9	−38, 30, 30
	664	6	−30, −6, 44
Right middle frontal gyrus	712	8	32, 24, 42
Right medial frontal gyrus	1480	9	6, 42, 18
Right cingulate gyrus	1704	32	2, 18, 34
Right claustrum	1776		26, 22, 2
Left middle occipital gyrus	416	19	−42, −70, 6
Right inferior parietal lobule	792	7	36, −58, 42
Left claustrum	880		−28, 24, 0
Right putamen	448		20, −4, 14
Left mediodorsal thalamus	1736		−4, −14, 10
Greater Activity in Schizophrenic Patients Than Controls			
Left superior frontal gyrus	440	6	−8, −14, 68
	1320	9	−2, 52, 24
Left inferior frontal gyrus	656	46	−40, 36, 12
Right medial frontal gyrus	424	10	8, 44, −12
Left precentral gyrus	752	6	−54, 4, 30
Left cingulate gyrus	2208	32	−2, 10, 40
Right superior temporal gyrus	584	41	38, −36, 6
Left inferior parietal lobule	1200	40	−54, −42, 42
Right lingual gyrus	800	18	14, −74, 6
Right insula	1136	13	38, 16, 4
Right amygdala	592		18, −4, −12
Greater Activity in Controls Than Schizophrenic Patients[b] (n=22)			
Right medial frontal gyrus	360	9	6, 42, 18
Left medial frontal gyrus	184	8	−12, 34, 36
Left middle frontal gyrus	240	6	−30, −6, 42
Left middle frontal gyrus	120	9	−40, 32, 28
Right cingulate gyrus	848	32	2, 18, 34
Left superior parietal lobule	224	7	−28, −70, 46
Right inferior parietal lobule	368	7	36, −60, 42

[a] Regions are listed in hierarchical order based on the following nested criteria: cortical to cerebellar to subcortical, rostral to caudal, dorsal to ventral, left to right, and large to small.
[b] Without N-back studies.

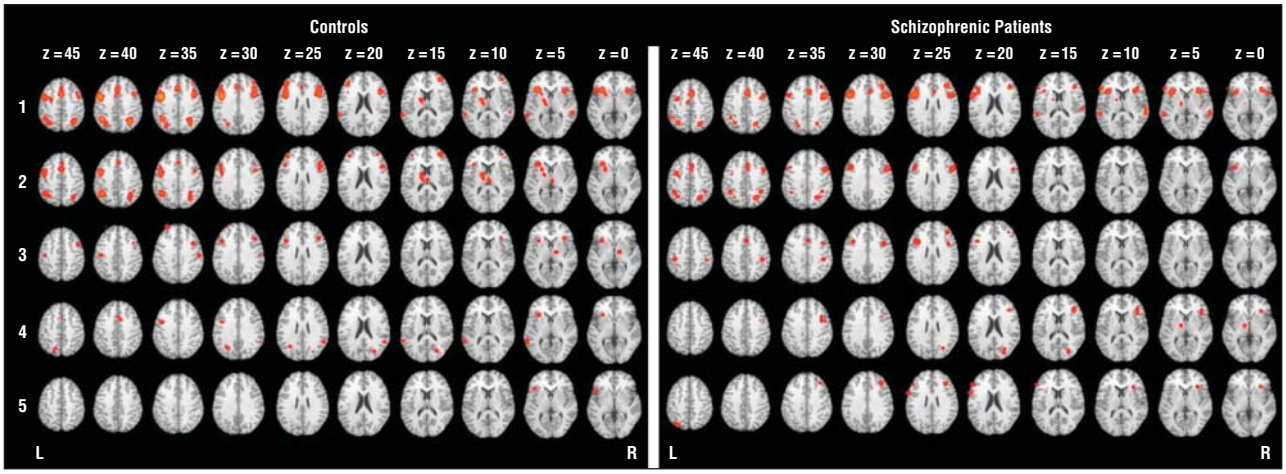

Figure 2. Brain regions with significant within-group activation by executive function task. L indicates left; R, right; 1, global; 2, N-back; 3, go/no-go; 4, Stroop; 5, delayed match to sample.

middle frontal gyrus (Table 2), suggesting that differences in the full 41-study sample were not inordinately determined by the N-back studies.

A large area near the rostral pole of the left PFC and areas in the left dorsal and ventral premotor cortex were activated to a greater degree in patients than in control subjects. This area is considerably smaller and located posterolateral to the left DLPFC area, which is impaired in patients. A restricted area in the left VLPFC and 2 midline frontal cortical areas were also observed. The largest of these was located in the dorsal ACC, posterior and dorsal to the ACC area where the patients were impaired, extending primarily into the suprajacent SMA. A smaller area was located in the ventromedial PFC. Posterior neocortical areas were found in the temporal and parietal cortex. Subcortical areas included the insula and amygdala, both in the right hemisphere.

TASK-WISE WITHIN-GROUP RESULTS

We identified which sets of tasks were associated with significant activity in a given brain region, within a given subject group (**Figure 2** and **Table 3**). We present the results in this manner, rather than enumerate separate active brain regions by task, to emphasize task-related neuroanatomic differences.

Controls

Subregions within the DLPFC were activated in the N-back and go/no-go but not in the delayed match-to-sample or Stroop tasks. The VLPFC was activated in the delayed match-to-sample task. The ACC was activated in the N-back and Stroop tasks. A large midline SMA/pre-SMA region was activated solely in the N-back task. The premotor cortex was activated in the N-back, go/no-go, and Stroop tasks. The primary somatosensorimotor cortex was activated only in the go/no-go task. In the temporal lobe, only the left middle temporal gyrus was activated during the Stroop task. In the parietal lobe, significant activation was observed in the right supramarginal gyrus in the Stroop tasks and in the left inferior parietal lobule in the N-back task. The precuneus was activated in the N-back and Stroop tasks. The left claustrum was activated in the N-back, go/no-go, and Stroop tasks. Cerebellar activation was observed (bilaterally) only in the N-back task. The thalamus was activated in the N-back (bilateral) and go/no-go (right thalamus) tasks.

Schizophrenic Patients

Subregions within the DLPFC were activated in the N-back, delayed match-to-sample, and go/no-go tasks. Conversely, the VLPFC was activated only in the Stroop task. The ACC was activated in the N-back and go/no-go tasks. The premotor cortex was activated in the N-back and Stroop tasks. The postcentral gyrus was activated in the Stroop task. In the parietal lobe, significant activation was observed in the superior parietal lobule in the N-back and delayed match-to-sample, in the inferior parietal lobule bilaterally in the N-back, and in the right hemisphere on the go/no-go tasks. The cuneus was activated in the Stroop task. Unlike controls, the patients showed activation in the insula with the N-back, delayed match-to-sample (right), and Stroop tasks. Cerebellar activation was observed only in the N-back task. The left thalamus was activated only in the Stroop task.

BETWEEN-GROUP GLOBAL RESULTS OF FRACTIONAL SIMILARITY NETWORK ANALYSIS

Areas of schizophrenic hypoactivation that co-occurred across the full set of studies included the bilateral DLPFC, the right ACC, and the left mediodorsal nucleus of the thalamus (**Figure 3** and **Table 4**). The bilateral claustrum represented a second set of co-occurring brain regions that were impaired in the patients.

Analysis revealed 2 regions where patients activated more than controls across all studies, including the left ACC and left inferior parietal lobule (Figure 3 and Table 4). As with the between-group analyses reported above, the ACC subregion was dorsal and posterior to the ACC subregion, where the patients exhibited impaired activity.

Table 3. Brain Regions With Significant Activation Within Healthy Control and Schizophrenic Patient Groups by Task

Brain Region[a]	Volume, mm³	Brodmann Area	Talairach Coordinates, x, y, z
N-Back in Controls			
Right superior frontal gyrus	1600	6	2, 8, 48
Left middle frontal gyrus	4888	6	–42, 2, 40
	720	10	–36, 40, 24
	408	6	–22, –12, 52
Right middle frontal gyrus	1104	10	36, 44, 16
Right inferior frontal gyrus	2072	9	46, 14, 22
Right precentral gyrus	1072	6	32, –8, 54
Right anterior cingulate gyrus	952	32	2, 24, 38
Left inferior parietal lobule	3384	40	–38, –54, 38
Right precuneus	2360	19	32, –62, 38
Left cerebellum declive	3024		–36, –68, –14
Left cerebellum, cerebellar tonsil	608		–36, –54, –38
Right cerebellum declive	1048		30, –64, –16
Right cerebellum anterior lobe	832		32, –56, –28
	568		0, –54, –28
Left claustrum	2240		–30, 20, 2
Left thalamus ventral anterior nucleus	1760		–12, –8, 12
Right thalamus	816		4, –22, 8
N-Back in Schizophrenic Patients			
Left middle frontal gyrus	1616	6	–32, –2, 48
	1568	9	–42, 14, 28
Right middle frontal gyrus	3272	9	46, 8, 34
Right anterior cingulate gyrus	1648	32	6, 18, 42
Right superior parietal lobule	1952	7	24, –64, 42
Left inferior parietal lobule	1240	40	–38, –48, –40
Right inferior parietal lobule	736	40	40, –46, 40
Left cerebellum declive	944		–36, –62, –16
	672		–6, –72, –14
Right cerebellum culmen	1304		38, –52, –18
Left insula	664	13	–36, 14, –2
Delayed Match to Sample in Controls			
Right middle frontal gyrus	840	11	28, 44, –10
Left inferior frontal gyrus	592	45	–40, 20, 4
Delayed Match to Sample in Schizophrenic Patients			
Left middle frontal gyrus	728	46	–50, 28, 20
Right middle frontal gyrus	1000	9	36, 30, 28
Left inferior frontal gyrus	856	9	–58, 6, 22
Left superior parietal lobule	520	7	–36, –70, 46
Right insula	688		30, 22, 2

(continued)

COMMENT

Using a quantitative meta-analysis of 41 functional neuroimaging studies of executive functioning in schizophrenia, we found evidence of a superordinate, general-purpose cognitive control network that is associated with executive dysfunction in schizophrenia. Within-group analysis of all of the 41 studies indicated that healthy controls and schizophrenic patients activated a similarly distributed cortical-subcortical network while performing executive tasks, including the DLPFC, ACC, VLPFC, premotor cortex, lateral temporal cortical areas, parietal areas, cerebellum, and thalamus. Nevertheless, in direct between-group comparisons, schizophrenic patients exhibited reduced activation in several key nodes of this network, including the bilateral DLPFC, right VLPFC, right dorsal ACC, pre-SMA, left ventral premotor cortex, posterior areas in the temporal and parietal cortex, and subcortical areas, such as the mediodorsal thalamus and putamen. These results did not appear to reflect the inordinate influence of N-back studies. Of these regions, the DLPFC, ACC, and mediodorsal thalamus showed significant co-occurrence in between-group comparisons.

Increased activation in a frontocingulate network has been widely reported during normal executive functions[60] and is consistent with models of cognitive control,[7,8] which propose that the lateral PFC provides top-down control to establish an optimal pattern of processing across the brain to support task-appropriate responding. Consistent with this view, individual differences in DLPFC activation often correlate with superior task performance among the healthy subjects in these studies.[61-63] Within this model, the ACC monitors performance, is sensitive to levels of conflict present during information processing, and serves to modulate the level of DLPFC task–related engagement in a dynamic man-

Table 3. Brain Regions With Significant Activation Within Healthy Control and Schizophrenic Patient Groups by Task (continued)

Brain Region[a]	Volume, mm³	Brodmann Area	Talairach Coordinates, x, y, z
Go/No-Go in Controls			
Left superior frontal gyrus	576	9	–28, 50, 34
Left middle frontal gyrus	648	9	–40, 14, 28
Right middle frontal gyrus	640	9	42, 22, 28
	640	6	42, 6, 48
Right inferior frontal gyrus	448	13	36, 22, 6
Right precentral gyrus	552	9	40, 8, 36
Left postcentral gyrus	464	3	–42, –22, 40
Right postcentral gyrus	512	2	52, –22, 34
Left claustrum	544		–30, 14, 0
Right thalamus	736		14, –14, 2
Go/No-Go in Schizophrenic Patients			
Left middle frontal gyrus	1776	9	–36, 12, 26
Right middle frontal gyrus	664	10	38, 36, 24
Right inferior frontal gyrus	792	9	40, 8, 30
Right anterior cingulate gyrus	712	32	2, 14, 38
Right inferior parietal lobule	752	40	42, –32, 38
Stroop in Controls			
Left precentral gyrus	728	6	–42, 0, 34
Right anterior cingulate gyrus	464	32	2, 14, 40
Left middle temporal gyrus	1072	21	–58, –48, 6
Right supramarginal gyrus	680	40	54, –50, 24
Left precuneus	560	7	–24, –64, 30
	416	7	–14, –66, 44
Right precuneus	680	31	26, –72, 18
Left claustrum	688		–28, 18, 4
Stroop in Schizophrenic Patients			
Right middle frontal gyrus	1840	46	40, 28, 14
Right precentral gyrus	696	6	36, 2, 36
Left postcentral gyrus	528	5	–20, –42, 66
Right cuneus	1048	18	24, –76, 18
Right insula	464	13	32, 16, –6
Left thalamus	672		–12, –12, 2

[a]Regions are listed in hierarchical order based on the following nested criteria: cortical to cerebellar to subcortical, rostral to caudal, dorsal to ventral, left to right, and large to small.

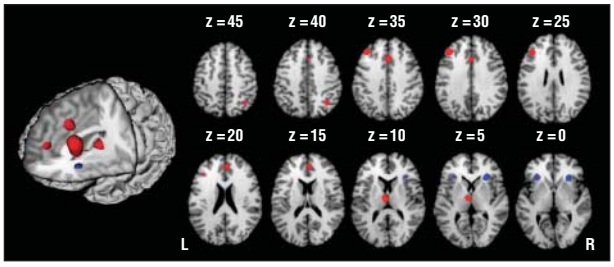

Figure 3. Co-occurring brain areas with significant differences between controls and schizophrenic patients across executive function studies. The 2 sets of clusters are arbitrarily indicated by color to distinguish them. L indicates left; R, right.

ner.[8,9] The consistent reduction of DLPFC and ACC activity observed in this meta-analysis is consistent with impairment in this dynamic cognitive control-related circuitry in schizophrenia. As noted, a broad network of frontal, subcortical, and posterior brain regions that support task performance were reduced in schizophrenic patients. Taken together, these findings are consistent with disrupted frontal-based top-down control functions (elaborated on in the Miller and Cohen "guided activation" model[7]) that lead to a disruption of processing

Table 4. Brain Regions With Significant Between-Group Differences in a Co-occurring Manner

Brain Region[a]	Volume, mm³	Brodmann Area	Talairach Coordinates, x, y, z
Greater activity in controls than schizophrenic patients			
Left middle frontal gyrus	1456	9	–38, 30, 30
Right middle frontal gyrus	696	9	6, 42, 18
Right anterior cingulate gyrus	792	32	2, 18, 34
Left claustrum	488		–28, 24, 0
Right claustrum	936		26, 22, 2
Left thalamus, medial dorsal nucleus	760		–4, –14, 10
Greater activity in schizophrenic patients than controls			
Left anterior cingulate gyrus	1256	32	–2, 10, 40
Left inferior parietal lobule	584	40	–54, –42, 42

[a]Regions are listed in hierarchical order based on the following nested criteria: cortical to subcortical, rostral to caudal, dorsal to ventral, left to right, and large to small.

across the distributed brain network supporting task performance.

In contrast, patients with schizophrenia showed relatively greater activity in a region in the VLPFC; a midline cortical region located in the ACC extending into the SMA, which was dorsal and posterior to the ACC area showing reduced activity; posterior and inferior cortical areas (in the temporal and parietal cortex); the insula; and the amygdala. It is possible that these regions are associated with a compensatory response and/or are recruited to support alternate strategies to support task performance. With impaired DLPFC regulation of the distributed network engaged by task demands, patients may increase engagement of other processes to maintain task performance, such as attentional, mnemonic, and performance monitoring functions. These would be expected to manifest as relative hyperactivations in the ventral, medial, or posterior cortical regions. In addition, amygdala and insula activation clusters could reflect a differing emotional reactivity to task demands. This account could be compatible with a popular inefficiency hypothesis, as the compensatory hyperactivations could reasonably be viewed as reflecting an excessive distribution of cortical activity that is more restricted to the DLPFC and its tight control of these areas under normal (ie, healthy) conditions. A second possibility is that this profile of activity increases and decreases constitutes a disease-specific variation in the topographic basis for cognitive control and related executive functions. In this scenario, the topography of activity engaged during performance of these tasks is displaced for patients, giving rise to areas of relative hypoactivity adjacent to those with relative hyperactivity. This pattern of results does suggest a few adjacent regions with this pattern, notably in the medial wall of the PFC; however, this is not a comprehensive pattern in the present results, which suggests that other factors are at work. In any event, the present results taken together strongly argue against a simple hypofrontality vs hyperfrontality account of the altered function of the frontal cortex in schizophrenia.

Within the healthy control group, the distributed cognitive control network was engaged comparably across various executive function tasks, including the lateral PFC; premotor cortex; posterior neocortical areas, such as the parietal cortex and precuneus; and the thalamus. There were nonetheless some interesting task-specific areas of activation, which may be related to particular demands on certain component cognitive processes in these tasks. These include medial PFC (ACC and SMA/pre-SMA) activation in the Stroop and N-back tasks, potentially a function of conflict-processing demands; lateral (neocortical) temporal lobe and supramarginal gyrus activation in the Stroop task, both likely a function of linguistic processing involved in this task; and cerebellar activation in the N-back task, which may be related to the degree of temporal sequencing in processing of stimuli in this task. Notably, delayed match-to-sample performance was unassociated with above-threshold DLPFC activation (though significant VLPFC activity was evident), suggesting that these tasks were effectively performed by controls using simple maintenance strategies, obviating the need for higher-order dorsal PFC–mediated control.

The degree of task-specific variation appeared roughly comparable in the schizophrenia group, with lateral PFC activation in each task and similar variation in the observation of activation in midline PFC areas; in posterior cortical areas, such as the parietal cortex and cuneus; and in other elements of this distributed circuit, such as the cerebellum and thalamus. Inferences regarding which task-related areas of activation are significantly different between the 2 subject groups are best appreciated in the direct between-group comparisons described above.

A few limitations in this study are apparent. Activation likelihood estimation requires that source reports present data in 3-dimensional coordinates in a standard brain space and excludes studies that report only region-of-interest findings. However, the vast majority of published neuroimaging studies, including those focused on schizophrenia, report voxel-wise analyses in standard brain space.[12,64] As a result, we included the largest set of studies of this kind to date in a quantitative meta-analysis. A further limitation is the relatively small set sizes for individual task types (other than the N-back). Therefore, results of the other major task types should be interpreted with caution. The future expansion of this primary source literature should enhance the reliability of meta-analytic approaches to these studies. Finally, in this type of meta-analysis, it would be generally desirable to have the capability to evaluate a range of study-wise factors that may be associated with variation in reported effects. These factors may include subject-specific factors, such as clinical or demographic factors or variation in sample size, and variation in data acquisition and analysis, which may affect both effect sizes and the brain topography of these effects. The considerable variation in study design and analysis and clinical measures used among the source studies (Table 1) unfortunately precludes a quantitative assessment of these factors. Given this variation, it is remarkable that a number of reasonably predictable and coherent results were found. This suggests a degree of robustness in the present results and that we have achieved a fair view of the landscape of this literature, which is a distinct advantage of meta-analysis in general.[10]

CONCLUSIONS

The association of deficits in executive cognitive functions with reduced functions of a frontal-cortical–based cognitive control system in the brain has important implications for both the pathophysiology of cognitive pathology in the illness as well as for the development of therapies targeting this disabling aspect of the illness. For instance, there could be a single or a few pathologic processes that manifest throughout this network that give rise to the observed findings. These processes could include (but are not limited to) developmental processes, which might include genes regulating neural development, and neurotransmitter elements that regulate signaling activity throughout this network, which could include systems like glutamate, γ-aminobutyric acid, and/or monoamines. These results do not rule out a multiple-hit model of underlying cellular/molecular pathology; rather, it seems unlikely that this pathology would manifest in a widely coincident yet independent gross anatomic pattern. An al-

ternative account of the present findings, which emphasizes the fractional similarity network analysis results, posits the DLPFC/ACC/mediodorsal thalamus triad as a core deficit, with the dysfunction elsewhere in the network as a downstream functional consequence of this disturbance. In any event, the robust meta-analytic results found across this heterogeneous set of studies reaffirms the reliability of functional magnetic resonance imaging to assess the functional neuroanatomy of schizophrenia. Treatment implications suggest that, to the extent that a unitary pathophysiological process is evident, a more unitary intervention strategy might be adopted to target the discrete neural system serving these general-purpose cognitive control functions.

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