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The functional neuroanatomy of schizophrenic subsyndromes

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ABSTRACT

Background. There is considerable variability between patients in their expression of the diverse range of symptoms encompassed by the syndrome of schizophrenia, which may modulate functional activation to cognitive processing.

Method. Here we investigate associations between schizophrenic subsyndrome scores, identified by factor analysis, and experimentally controlled brain activation. Five factors were defined by rotated principal components analysis of PANSS rating scale measurements in 100 patients with schizophrenia. A subsample of 30 patients and a group of 27 comparison subjects were studied using functional magnetic resonance imaging (fMRI) during the performance of two periodically designed cognitive activation experiments: verbal working memory and psychomotor sequencing.

Results. Factor analysis replicated the five dimensions consistently reported. Within the patient group, power of activation by working memory was negatively associated with global symptom severity in left lingual and temporo-parietal cortices; negatively associated with positive subsyndrome scores in left inferior frontal and superior temporal cortices and basal ganglia; and positively associated with negative subsyndrome scores in lateral and medial premotor cortex. No relationship was observed between subsyndrome scores and functional activation during the motor task. Between-group comparisons demonstrated reduced power of response to the working memory task by patients in bilateral dorsolateral prefrontal and left pre- and post-central cortices.

Conclusions. In this study we observed task-specific modulation of functional response associated with symptom expression in schizophrenia. Our findings are compatible with previous empirical findings and theoretical conceptualization of human brain function, in terms of capacity constraints on activation in the face of competing demands from pathological and task-related cognitive activity.

INTRODUCTION

Dimensional models of schizophrenia have attempted to address its phenomenological heterogeneity by identifying subsyndromes of co-occurring symptoms. Using factor analysis of symptom ratings, Liddle (1987*a*) identified three subsyndromes of schizophrenia, labelled psychomotor poverty, reality distortion and disorganization, which have been widely replicated. Functional deficits in left dorsolateral and right ventrolateral prefrontal cortex, were hypothetically associated with psychomotor poverty and disorganization, respectively; deficits in temporal lobe function were predicted in the reality distortion syndrome (Liddle, 1987*b*). Using PET, Liddle *et al.* (1992) provided the first direct evidence of distinct neurobiological substrates for these three dimensions of psychopathology

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in schizophrenia. Replication of these pioneering studies has provided partial corroboration (Ebmeier *et al*. 1993; Kaplan *et al*. 1993; Schroder *et al*. 1996); there are several methodological reasons that may explain some of the inconsistencies in these latter studies.

As suggested by Liddle *et al*. (1994), 'The studies that have found three syndromes have not included the entire gamut of schizophrenic symptoms'. Clinical rating scales that omit some of the full range of symptoms may yield a factor structure that distorts the underlying pattern of relationships between symptoms, given that the factor structure is generated on the strength of relationships between items that load on different factors, as well as relationships between items within a factor (Peralta & Cuesta, 1998). Factor analyses of the Positive and Negative Syndrome Scale (PANSS) (Kay *et al*. 1987), which provides a more comprehensive symptomatic assessment, have reliably reported a five factor model (Lindstrom & von Knorring, 1994; White *et al*. 1997). It should be noted, however, that while there is general agreement across factor analytic assessments of symptoms identified using the PANSS, the precise item composition of these factors varies to some extent across studies, and more ambivalent items that tend to load across multiple dimensions are occasionally excluded from the extracted factor structure. The cognitive dimension, in particular, shows a variable loading of items.

Another potential source of variability is the use of resting or baseline measures of cortical physiology, which is highly variable across individual subjects. Variations in rCBF measures may, therefore, simply reflect the subjective experience of the procedure itself, rather than underlying cerebral pathology (Andreasen *et al*. 1997). It has also been suggested that there is no reason *a priori* why low resting rCBF should relate to a lack of functional activation under task-related demand; indeed, it is conceivable that with a relatively lower starting point there is potential for greater increases in activity (Frith *et al*. 1995). Analogous to the use of cardiac stress tests in clinical medicine, cerebral functional deficits may only become apparent under conditions of increased physiological load (Berman, 1987). Hypofrontality, for example, has been demonstrated during the performance of cognitive tasks in patients who did not demonstrate hypofrontality in measurement of resting perfusion levels (Volkow *et al*. 1987; Zemishlany *et al*. 1996).

Here, we have addressed these two issues by applying factor analysis to PANSS ratings on a sample of 100 schizophrenic patients, and using their scores from each of the five factors to predict power of cerebral activation by two experimentally controlled tasks in a subsample of 30 patients. We predicted: (*i*) replication of established five symptom dimensional structure by factor analysis; (*ii*) consistent with previous imaging studies of working memory, schizophrenic patients would exhibit a hypofrontal response, as a group, compared to healthy volunteers (Fletcher *et al*. 1998; Bullmore *et al*. 1999*a*); and (*iii*) within the schizophrenic group, symptom dimensions would be differentially associated with power of functional response to the working memory task, given previous associations between working memory and psychotic symptomatology.

METHOD

Clinical and demographic data

A group of 100 patients with a diagnosis of schizophrenia according to DSM-IV criteria was recruited from the patient population of the Bethlem Royal and Maudsley NHS Trust for the assessment of clinical symptomatology using the PANSS. This was assessed by two clinicians trained on the use of these scales, and having established $>0{\cdot}8$ inter-rater reliability. The mean age of the group was 35 ($\pm$S.D. 9·2) years. Mean duration of illness was 10·24 ($\pm$10) years, with a mean age of onset of 24·9 ($\pm$6·5) years. Mean scores of the PANSS positive, negative and general psychopathology subscales were 15·8 ($\pm$7·2), 16·6 ($\pm$7·2) and 32·7 (11·2). There were 77/100 males in the group.

A subset of 30 patients was randomly sampled for fMRI scanning. For this subset of patients, mean duration of illness was 13 ($\pm$9·8) years, with a mean age of onset at 23·9 ($\pm$6·3) years, and mean dose of typical antipsychotic drugs was 327·3 ($\pm$205·3) chlorpromazine-equivalent mg/day. Mean scores on the PANSS positive, negative and general psychopathology subscales (rated within 1 week of the fMRI scan) were 11·7 ($\pm$6·1), 14·6 ($\pm$7·1) and 26·3 ($\pm$10·3) respectively.

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A group of 27 healthy volunteers without personal or familial neurological or psychiatric history also participated in the fMRI aspect of the study. There was no significant difference in the mean age of the scanned patient and comparison groups (36·9 (±9·2) and 35·1 (±9·9) years respectively). There were 27/30 male subjects in the patient group and 21/27 males in the comparison group. All subjects were right-handed. After comprehensive description of the study, written informed consent was obtained from all participants. Scanning procedures were in accordance with the guidelines of the Bethlem Royal & Maudsley Hospital (Research) Ethical Committee.

Factor analysis

Orthogonal rotation of principal components with eigenvalues >1 by the equamax procedure was used to identify five subsyndromal factors in the standardized PANSS measurements made on the full sample of 100 patients (see Nunnally, 1994) for general introduction to factor analysis). Factor scores were derived from this analysis for each of the 30 patients in the fMRI subsample. Global symptom severity was measured by summing the five subsyndrome scores for each subject.

Image acquisition

Gradient-echo echoplanar MR images were acquired using a 1.5 Tesla GE Signa System at the Maudsley Hospital, UK. In each of 14 non-contiguous planes parallel to the inter-commissural (AC–PC) line, 100 T2*-weighted MR images depicting BOLD contrast were acquired: TE = 40 ms, TR = 3 s, in-plane resolution = 3·1 mm, slice thickness = 7 mm, slice skip = 0·7 mm.

Image analysis

After estimation and correction of head motion during scanning (Bullmore *et al.* 1999*b*), experimentally determined power was estimated in each fMRI time series by sinusoidal regression, described in detail elsewhere (Bullmore *et al.* 1996; Brammer *et al.* 1997). Briefly, the power of periodic signal change at the (fundamental) frequency of stimulation was estimated by the iterated least squares fitting of a sinusoidal regression model at each voxel in standard space (Talairach & Tournoux, 1988). The fundamental power quotient (fundamental power divided by its standard error) was estimated at each voxel. If the median fundamental power quotient exceeded the critical value of the median fundamental power quotient obtained by randomization, that voxel was considered generically activated with a probability of false positive activation of $\alpha < 0{\cdot}001$.

To estimate the difference in mean power of response between the groups of patients and comparison subjects, we fitted the following one-way ANCOVA model at each intracerebral voxel:

$$P = \mu + \beta_1 \mathrm{G} + \beta_2 \mathrm{Age} + \varepsilon. \quad (1)$$

Here, μ is the overall mean power, G is a vector coding group membership, Age is the subject's age, and ε is an error. The null hypothesis that the coefficient $\beta_1 = 0$ was tested by permutation at cluster level, as described in detail elsewhere (Bullmore *et al.* 1999*c*). Briefly, the procedure was as follows: a map of the standardized coefficient $\beta_1/\mathrm{SE}(\beta_1)$ was thresholded so that if $|\beta_1/\mathrm{SE}(\beta_1)| > 2$, the voxel value was set to $|\beta_1/\mathrm{SE}(\beta_1)| - 2$. This resulted in a set of suprathreshold voxel clusters, spatially contiguous in two dimensions, each of which can be described in terms of its mass or the sum of suprathreshold voxel statistics it comprises. The 2D mass of each cluster was tested against a null distribution ascertained by repeated random permutation of the vector coding group membership in Eq (1), followed by thresholding of the standardized voxel statistic map and generation of 2D clusters under the null hypothesis (Bullmore *et al.* 1999*c*).

To estimate the association between power of response and subsyndromal scores within the group of patients, we fitted the following multiple regression model at each intracerebral voxel:

$$P = \mu + \beta_1 \mathrm{S1} + \beta_2 \mathrm{Age} + \varepsilon. \quad (2)$$

Here, S1 indicates the vector of scores on the first of the five subsyndromes separately modelled in this way; the other abbreviations are as before. The methods of inference used in the between-group comparison were identically applied to identify voxel clusters where the association between subsyndrome scores and power of response was significant.

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For the voxel-wise hypothesis tests conducted for generic brain activation mapping, a one-tailed probability of type 1 error $\alpha < 0{\cdot}001$ was adopted as the threshold for significance. For the cluster-wise hypothesis tests conducted for within- and between-group comparisons, a two-tailed probability of type 1 error $\alpha < 0{\cdot}01$ was adopted as the threshold for significance. This more lenient threshold for cluster-level testing is justified by the much smaller number of tests entailed at cluster level. Thus, for each of the maps reported here, the expected number of false positive clusters (number of clusters tested multiplied by α) was less than or equal to 1 over the whole map.

Cognitive paradigms

Five blocked periodic cycles of two contrasting conditions were presented in 30 s epochs, for 5 min for two experiments (order of presentation pseudo-randomized). Accuracy and reaction time were monitored by button press.

Verbal working memory

Baseline condition: the participants viewed a series of 11 letters, presented individually (inter-stimulus interval (ISI) = 2·3 s), and were required to press a button in response to the letter 'X'. Activation condition: the participants viewed a series of 11 letters and were required to press the button if the currently presented letter was the same as that presented two trials previously.

Psychomotor task

Baseline condition: the subject viewed the word 'REST' visually presented for 0·5 s (ISI 2·5 s). Activation condition: the subject viewed the word 'MOVE', paced identically to the stimulus in the control condition; in response to the visual cue, subjects were required to move a joystick using the right hand, which was secured in the left hand, in one of four possible directions (up, down, left or right); subjects were required to make the sequence of movements as random as possible, based on preliminary findings from pilot data indicating that motor response selection elicited more robust activation of medial and lateral motor cortical areas than repetitive movements, consistent with previous findings (Deiber *et al.* 1991; Touge *et al.* 1995).

RESULTS

Subsyndromal factor structure

Five principal components, with eigenvalues >1, accounted for 67·5% of the total variance. After rotation these factors were identified as negative, positive, excited, cognitive and depressed subsyndromes based on the symptom loadings (Table 1) and reference to the prior literature (Lindstrom & von Knorring, 1994; White *et al.* 1997). A close correspondence was observed between the loading of items of the five dimensions in this study, and that reported in previous studies. However, it is notable that the conceptual disorganization item (P2), generally observed to load on the 'cognitive' dimension, loaded on the first dimension, labelled the negative factor in this study. There were no significant correlations between any of the five factors and any demographic variables (two-tailed probability $\alpha < 0{\cdot}05$).

Behavioural data

Patients correctly identified 80% of targets in the working memory task on average; however, this was significantly less than the mean accuracy of the control group (96%). Patients also had significantly slower reaction times for both the working memory task, the working memory control task and the psychomotor task; see Table 2 for details. There were no significant correlations between any of the five subsyndromal factors and any of the behavioural measures of task performance (two-tailed probability $\alpha < 0{\cdot}05$).

fMRI data

Generic brain activation maps

Verbal working memory

Both groups demonstrated significant median power of activation in three main brain regions: (*i*) supplementary motor area (SMA) extending inferiorly to cingulate gyrus; (*ii*) dorsolateral prefrontal cortex (DLPFC) extending inferiorly to ventrolateral prefrontal cortex and superiorly to lateral premotor cortex; and (*iii*) parietal cortex, extending from the angular and supramarginal gyri to precuneus and dorsal occipital gyri medially and superiorly. Frontal and parietal regions were activated bilaterally (see Table 3).

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Table 1. *Rotated component loadings: according to the recommendations of Nunnally* (1994), *and given the relatively small number of patients included relative to the number of PANSS items, only those items whose communality was* >0·5 *are reported*

Factor label	Description	Item	Component 1	2	3	4	5	% Total variance	Cronbach's alpha
Negative	Passive/apathetic social withdrawal	N4	0·804					41·2	0·91
	Lack of spontaneity and flow of conversation	N6	0·775						
	Emotional withdrawal	N2	0·706						
	Blunted affect	N1	0·698						
	Active social withdrawal	G16	0·682						
	Poor rapport	N3	0·560						
	Conceptual disorganization	P2	0·506						
	Disturbance of volition	G13	0·501						
Positive	Grandiosity	P5		0·787				9·6	0·86
	Unusual thought content	G9		0·704					
	Delusions	P1		0·654					
	Preoccupation	G15		0·527					
	Hallucinatory behaviour	P3		0·510					
Excited	Hostility	P7			0·787			8·0	0·84
	Poor impulse control	G14			0·779				
	Poor attention	G11	0·515		0·526				
Cognitive	Somatic concern/delusions	G1				0·706		5·1	0·79
	Mannerisms and posturing	G5				0·616			
	Lack of judgement and insight	G12		0·519		0·583			
	Difficulty in abstract thinking	N5				0·515			
	Stereotyped thinking	N7				0·513			
	Disorientation	G10				0·508			
Depressive	Anxiety	G2					0·834	3·7	0·81
	Tension	G4					0·742		
	Guilt feelings	G3					0·731		
	Depression	G6					0·652		

Table 2. *Behavioural data for the verbal working memory and psychomotor tasks in patient and control groups* (*s.d. in parentheses*)

Group	Working memory condition targets identified (maximum = 11)	Reaction time (s) Working memory control condition	Working memory condition	Psychomotor task
Patient	8·8 (2·5)	0·61 (0·18)	0·72 (0·12)	0·56 (0·2)
Control	10·58 (0·78)	0·49 (0·11)	0·57 (0·08)	0·42 (0·08)
t statistics	$t = 3{\cdot}5$, df = 52***	$t = 4{\cdot}02$, df = 52****	$t = 3{\cdot}8$, df = 52****	$t = 3{\cdot}07$, df = 50**

** $P < 0{\cdot}01$; *** $P < 0{\cdot}001$; **** $P < 0{\cdot}0001$.

Psychomotor task

Both groups demonstrated significant median power of activation in the cerebellum bilaterally, the supplementary motor area and pre- and post-central gyrus bilaterally, extending caudally into adjacent parietal cortex. The patients additionally showed activation of inferior and middle frontal gyri bilaterally (see Table 3).

Between group comparisons

Verbal working memory

In comparison to the control group, schizophrenic patients demonstrated significant reduction of mean power in the dorsolateral prefrontal cortex bilaterally (Brodmann Area (BA) 9/46; Talairach co-ordinates (*x*, *y*, *z* mm): 30, 42, 28 and −41, 26, 32) and left pre-central gyrus (BA4; −43, −11, 50) (see Fig. 1).

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Table 3. *Main regional foci of generic activation in the working memory and psychomotor tasks in patients and controls*

				Controls				Patients			
					Talairach co-ordinates				Talairach coordinates		
Task	Region	BA	L/R	No. of voxels	*x*	*y*	*z*	No. of voxels	*x*	*y*	*z*
Working memory	Posterior parietal cortex/ precuneus	40/39/7/19	L/R*	412	−42	−55	42	376	49	−31	42
	Dorsolateral prefrontal	9/44	L	74	−43	3	37	3	−38	14	31
	cortex	46/10	R	24	38	42	15	26	55	8	26
	Inferior frontal gyrus	45	L	11	−32	19	4	12	−43	14	9
		45	R	10	52	14	20	7	46	8	9
	SMA/anterior cingulate	6/32	Med	90	3	8	48	20	6	17	42
	Lateral premotor cortex	6	L	43	−43	−3	42	14	−32	0	48
	Extrastriate cortex	18	L	56	−38	−69	−13	7	−38	−59	−13
		18	R	23	32	−64	−13	4	38	−64	−13
	Cerebellum	—	L	3	−12	−78	−18	26	−6	−72	−13
			R	5	29	−64	−18	10	23	−58	−13
Psychomotor	Cerebellum	—	L/R	397	17	−53	−13	320	23	−56	−13
	Post-central gyrus/posterior	1/2/3/40	L(L/R)*†	287	−38	−28	48	1198	−35	−39	48
	parietal cortex		R	226	43	−36	48				
	SMA	6	Med	77	3	−8	48	376	43	0	37
	Pre-central gyrus	6	R					103	46	3	9
			L					19	−38	6	9
	Inferior frontal gyrus	44	R					78	52	8	26
			L					14	−49	8	31
	Middle frontal gyrus	9	L					35	−20	35	37
			R					7	40	31	26

* Coordinates represent the centroid of a spatially dispersed three dimensional cluster, covering several brain regions.
† Laterality differs across groups; patients laterality in brackets.

Psychomotor task

The patient group demonstrated significant enhancement of mean power in right lateral premotor area (BA6; 42, 0, 45) in comparison to the control group.

Associations between brain function, total symptom scores and subsyndrome scores

Verbal working memory

Global symptom severity scores were negatively associated with the power of functional response in the left lingual gyrus and left superior temporal gyrus, extending superiorly into inferior parietal cortex (see Figs. 1 and 2 and Table 4). Negative subsyndrome scores were positively associated with power of response in lateral premotor cortex bilaterally, SMA and right posterior parietal cortex (see Figs. 1 and 2 and Table 4). Positive subsyndrome scores were negatively associated with power of response in several left hemisphere regions including inferior frontal gyrus, middle and superior temporal gyri, inferior parietal cortex, lateral premotor cortex, and the caudate nucleus. There was also a negative association in right middle temporal gyrus extending inferiorly to superior occipital gyrus (see Figs. 1 and 2 and Table 4). Excited subsyndrome scores were negatively associated with power of response in left middle and superior temporal gyrus, posterior parietal cortex and precuneus, and in left middle frontal gyrus, SMA and right angular gyrus; (see Table 4). Cognitive subsyndrome scores were negatively associated with functional response in left temporal, right inferior frontal gyrus, right cingulate gyrus, supramarginal gyrus bilaterally, and left lateral premotor cortex; (see Table 4). Depressive subsyndromes scores were not significantly associated with functional response.

Psychomotor task

There were no clusters of significant association between functional response to this task

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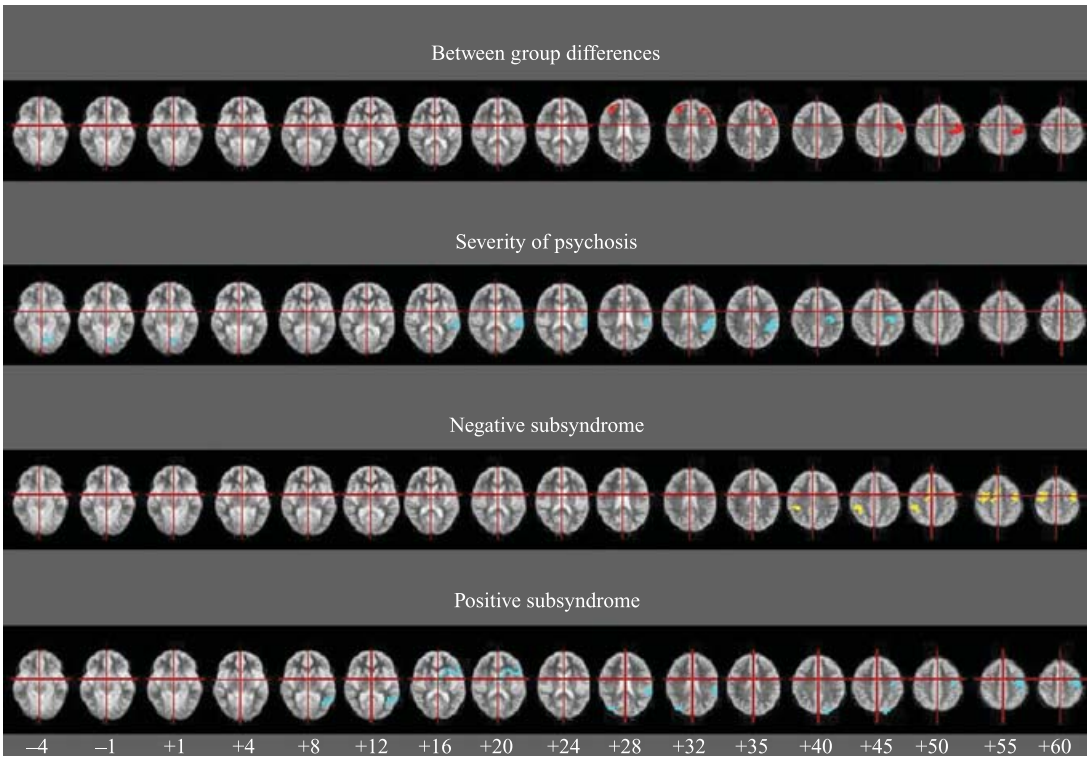

FIG. 1. Maps of significant between-group differences in power of response to a verbal working memory task (top row) and of significant associations between functional response to working memory and global and subsyndrome scores. Top row, red voxels indicate clusters of significantly reduced power in the group of patients with schizophrenia ($N=30$) relative to a group of comparison subjects ($N=27$); second row, blue voxels indicate clusters of significant negative association between global severity of psychosis (summed factor scores) and functional response; third row, yellow voxels indicate clusters of significant positive association between severity of negative subsyndrome and functional response; fourth row, blue voxels indicate clusters of significant positive association between severity of positive subsyndrome and functional response. The distance of each map above the intercommissural line in the standard space of Talairach & Tournoux (1988) is given in millimeters below. The right side of the brain is shown on the left side of each map.

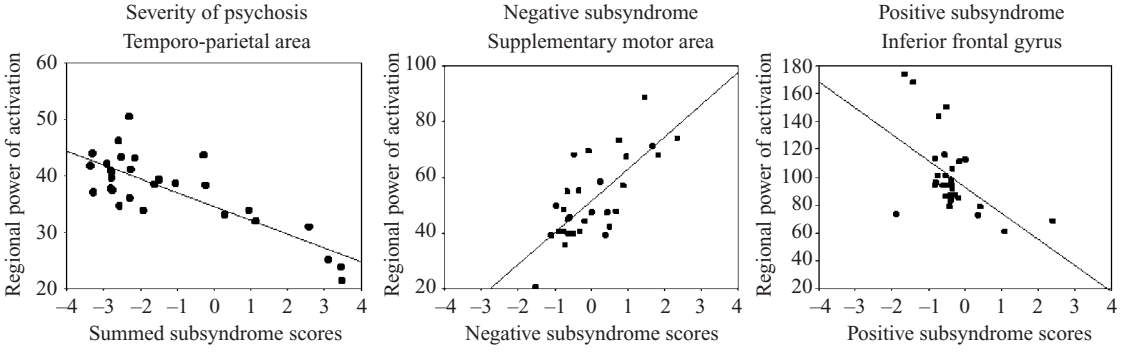

FIG. 2. Scatter plots of regional activation *versus* global, negative and positive subsyndrome scores. Left, negative association between global severity and power of response in left temporo-parietal cortex ($R^2=0{\cdot}58$); middle, positive association between negative subsyndrome and power of response in supplementary motor area ($R^2=0{\cdot}54$); right, positive association between positive subsyndrome and left inferior frontal gyrus ($R^2=0{\cdot}28$). Note that the *y* axes for these plots are differently scaled, as a result of the differences in the amplitude of response across these regions.

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Table 4. *Talairach coordinates of clusters showing significant correlation between power of functional response during the working memory task and subsyndrome scores*

	Negative correlations						Positive correlations					
				Talairach coordinates						Talairach coordinates		
Subsyndrome	Region	L/R	BA	*x*	*y*	*z*	Region	L/R	BA	*x*	*y*	*z*
Negative	No correlation						Lateral premotor area	R	6	37	−4	55
								L	6	−42	−4	55
							Posterior parietal cortex	R	40	41	−33	40
							SMA	Med	6	6	0	50
Positive	Inferior frontal gyrus	L	44/45	−40	13	20	No correlation					
	Middle/superior temporal gyrus	L	21/22	−50	−53	12						
	Inferior parietal lobe/superior temporal gyrus	L	40/42	−57	−33	28						
	Middle temporal/occipital gyrus	R	39/19	−57	−33	28						
	Caudate nucleus	L	—	−10	13	16						
	Lateral premotor area	L	6/4	−41	−9	55						
Excited	Middle/superior temporal gyrus into parietal cortex and precuneus*	L	21/22/42/40/7/19	−40	−65	32	No correlation					
	Middle frontal gyrus	L	9	−45	10	40						
	SMA	Med	6	3	−3	55						
	Angular gyrus	R	39	41	−64	32						
Cognitive	Superior/middle temporal gyrus	L	22/39	−42	−52	12	No correlation					
	Inferior frontal gyrus	R	44	50	6	20						
	Cingulate gyrus	R	30	23	−33	20						
	Supramarginal gyrus	L	39/40	−43	−32	32						
		R	39/19	36	−69	32						
	Lateral premotor cortex	L	6	−33	4	55						
Depressed	No correlation						No correlation					
Symptom severity	Superior temporal gyrus into posterior parietal cortex*	L	22/40	−47	26	34	No correlation					
	Lingual gyrus	L	18	−13	−67	−4						

Coordinates are from Talairach & Tournoux (1988).
* Coordinates represent the centroid of a spatially dispersed three dimensional cluster, covering several brain regions.

and any of the global or subsyndromal factor scores.

DISCUSSION

This study demonstrated anatomically distinct psychophysiological associations between global and subsyndromal symptom scores and power of fMRI activation by a verbal working memory task in 30 patients with schizophrenia. No relationship was observed between symptom expression and cerebral response to the psychomotor task, indicating a degree of specificity to the relationship observed between symptomatic status and cognitive activation during the working memory task. These data therefore provide complementary information to previous studies of associations between symptoms of schizophrenia, which have focused on resting cerebral activity, by demonstrating the nature of symptomatic modulation of brain function under cognitive challenge.

The regional specificity of the psychophysiological associations observed between symptom dimension/severity and fMRI-measured cognitive activation is compatible with previous studies of resting state neurophysiology in schizophrenia. Global symptom severity was associated with functional activation in the left superior temporal gyrus and left lingual gyrus. The first of these results is comparable to previous associations reported between summed subsyndromal scores and resting cerebral perfusion demonstrated in left medial temporal

lobe (Friston *et al*. 1992) and also between total BPRS scores and resting glucose metabolism in left superior temporal gyrus (DeLisi *et al*. 1989). These studies provide convergent evidence that left temporal lobe function seems especially sensitive to the overall severity of schizophrenic psychosis. The association observed in this study between negative subsyndrome scores and power of functional response in bilateral and medial premotor cortex is consistent with several studies examining resting CBF/metabolism, which have also reported an association between negative symptoms and frontal resting activity (Volkow *et al*. 1987; Liddle *et al*. 1992; Wolkin *et al*. 1992; Ebmeier *et al*. 1993; Kawasaki *et al*. 1996; Schroder *et al*. 1996). Positive subsyndrome scores were associated with the power of functional response in several left hemispheric brain regions including inferior frontal gyrus, middle/superior temporal gyrus, inferior parietal cortex, premotor cortex and caudate nucleus. Previous studies which have examined the relationship between co-occurring positive symptoms and resting cerebral state have inconsistently found association with temporal lobe activity (Liddle *et al*. 1992; Ebmeier *et al*. 1993; Kaplan *et al*. 1993; Kawasaki *et al*. 1996; Schroder *et al*. 1996). However, auditory hallucinations have been consistently associated with abnormal blood flow in interconnected left hemispheric language areas, such as inferior frontal and superior temporal gyri, and/or SMA (DeLisi *et al*. 1989; McGuire *et al*. 1993; Suzuki *et al*. 1993).

We also observed significant association between functional response to the working memory task and patients' scores on both the excited and cognitive subsyndromes, but not the depressive subsyndrome. There is similarity between these observed patterns of regional associations, and the findings reported by the only previous study to investigate the neurobiological basis of the PANSS, which measured resting state perfusion (Kawasaki *et al*. 1996). However, given the small amount of variance accounted for by these subsyndromes in this sample, and the lack of previous research to constrain interpretation, these latter findings should be regarded cautiously, and require replication.

Although the regional localizations of the psychophysiological correlations observed in this study generally correspond with the prior literature on resting state perfusion/metabolism in schizophrenia, the direction of associations in our study is reversed relative to the resting state literature. We suggest that these apparent discrepancies may be resolved within the theoretical context of a capacity model for cortical function (Just & Carpenter, 1992; Just *et al*. 1996) (schematically illustrated in Fig. 3). Briefly, this model suggests that different cognitive tasks may compete for common, capacity-limited neural resources. As the demands on processing resources increase, there is increasing functional activation of the brain regions specialized to perform the relevant tasks until a capacity limit is reached, at which point activation by one or more of the competing tasks is attenuated. Cognitive activation studies incorporating parametric modulation of working memory load (Callicott *et al*. 1999) and dual-task performance interference (Klingberg, 1998) provide supporting evidence for this model of brain function. Perturbations of endogenous or baseline activity may also compete for neural resources with exogenous or experimentally administered cognitive tasks; for example, a negative correlation between focal activation during visual stimulation and baseline rCBF has recently been

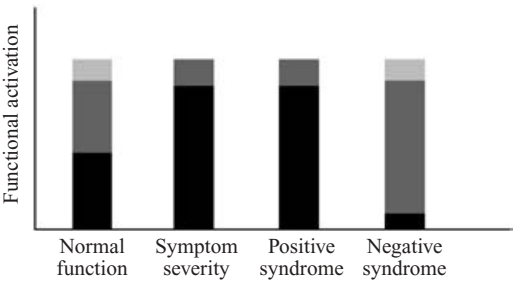

FIG. 3. Schematic representation of a simple capacity model of cortical function. The model assumes a fixed capacity for cognitive processing in a given cortical region. Endogenous processing demands due to 'resting' brain activity can compete for capacity-limited neural resources with exogenous, experimentally-controlled processing demands. The power of functional activation, as measured here by fMRI, is inversely proportional to the amount of total capacity consumed by endogenous processes. Thus, patients with positive symptoms may have increased endogenous activity in left perisylvian cortex and concomitantly attenuated power of functional activation by exogenous tasks, such as verbal working memory, which make competitive demands on these regions. Likewise, patients with negative symptoms may have reduced endogenous activity in premotor cortex and concomitantly increased power of functional activation of this region by a competitive experimental task. (▒, Functional reserve; ■, exogenous task-related activity; ■, endogenous activity.)

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demonstrated in healthy volunteers (Kastrup *et al*. 1999).

In extending this model to the psychopathological literature, we propose that psychotic symptoms represent an endogenous demand on cortical processing resources which may be competitive with exogenous or experimental task demands. Thus, it is clear from studies of 'resting' brain activity in schizophrenic patients that positive symptoms are associated with a regionally-specific increase in endogenous activity of superior temporal and inferior frontal cortex and SMA (DeLisi *et al*. 1989; McGuire *et al*. 1993; Suzuki *et al*. 1993). The capacity model predicts attenuated activation of these regions by competitive tasks, i.e., tasks which would normally activate these regions strongly, in patients with positive psychotic symptoms. Indeed it has previously been shown that patients with a history of auditory hallucinations have attenuated activation of frontal and temporal regions in response to a verbal self-monitoring task (McGuire *et al*. 1995), and attenuated activation of the auditory cortex in response to external auditory stimulation (David *et al*. 1996; Woodruff *et al*. 1997). Our finding of a negative association between positive subsyndrome scores and power of activation by a working memory task in frontal and temporal cortex is likewise compatible with the predictions of the capacity model.

Applying the same logic to interpretation of our results on negative subsyndrome scores, we conclude that endogenous processing demands on lateral promoter cortex may be reduced in patients with severe negative symptoms, so that the capacity available to process an exogenously presented working memory task is increased, and power of activation by the experimental task is also increased. Similarly, our results on global symptom severity would suggest that schizophrenic symptoms generally impose an endogenous processing demand on left superior temporal and ventral occipital cortices.

It should be noted that in this study we did not directly measure baseline activity, and therefore these predictions, based on a simple capacity model of cortical function, are preliminary but potentially testable in future studies combining variable measures of exogenous task load, and resting baseline activity. The implication of our current findings, with reference to previous studies of the effect of schizophrenia on resting activity, is that symptom expression likely involves an interactive effect on both resting and activated states, the former compromising the latter, and that this is dependent on the nature of the neurocognitive requirements and neural resources engaged.

Finally, it is noteworthy that the significant between-group differences in activation of frontal cortex by the working memory task were not located in the same regions of frontal cortex that demonstrated significant psychophysiological associations with subsyndrome scores. One possible explanation is that relatively reduced power of activation in dorsolateral prefrontal cortex, or 'hypofrontality', in these data may be related to the relatively poor behavioural performance of the patients on the verbal working memory task, as reported previously (Fletcher *et al*. 1998). The differences in location of hypofrontality and psychophysiological associations are likewise compatible with the lack of correlation between subsyndrome scores and behavioural measures of task performance, suggesting that cognitive impairment and psychotic symptom severity are not strongly linked and may have anatomically dissociable neural correlates (Honey *et al*. 2002). The possibility of an interaction between symptom status, cognitive performance and neurophysiological response was not tested in these data, and remains an intriguing possibility for further study.

In summary, we have reported anatomically distinct psychophysiological associations between global and subsyndromal symptom scores and power of fMRI activation by a verbal working memory task in a sample of 30 patients with schizophrenia. We have generally interpreted these associations, in the light of complementary prior studies on 'resting' blood flow or metabolism, as indicating competition for limited cortical capacity between exogenous (experimental) and endogenous (psychopathological) processes in patients with schizophrenia.

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