

Dysfunction of a distributed neural circuitry in schizophrenia patients during a working-memory performance

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ABSTRACT

Background. In a recent longitudinal study of first-episode schizophrenia patients, we found that while dysfunction of the right dorsolateral prefrontal cortex (DLPFC), right thalamus, left cerebellum and cingulate gyrus normalized with antipsychotic treatment and significant reduction in symptomatology, the left DLPFC, left thalamus, and right cerebellum remained disturbed. In the present study we investigated whether these abnormalities are also present in clinically stable, relatively well-functioning schizophrenia patients in comparison to control subjects during performance of the N-back working-memory task.

Method. Twelve schizophrenia and 12 control subjects completed the study. The functional images collected during scanning were analyzed using a random-effects model in a restricted set of six regions of interest (ROIs). In addition, the exploratory search in the entire brain volume was performed.

Results. The ROI analyses revealed relative underactivation in the region of the left DLPFC and the right cerebellum, as well as overactivation in the left cerebellum. The exploratory whole-brain search exposed additional overactivation in the medial frontal, anterior cingulate, and left parietal cortices.

Conclusions. The present study provides evidence of significant underactivations in stable schizophrenia patients in regions that we have previously observed to be dysfunctional in acutely psychotic and partially remitted patients, together with extensive overactivations in several regions that potentially reflect some compensatory mechanism or increased effort on the working-memory task.

INTRODUCTION

A rapidly growing number of functional neuroimaging investigations of schizophrenia has revealed a wide variety of findings over the years. This diversity can be partly attributed to differences in the clinical status of patients being tested and their performance on a given task relative to control subjects, as well as to the

choice of a particular cognitive task and neuroimaging technique. However, even when only recent fMRI findings of working memory in schizophrenia are taken into consideration, we are struck by the apparent inconsistencies. For example, relative to control subjects, schizophrenia patients showed diminished prefrontal cortex (PFC) activation during performance of the auditory Word Serial Position Task (Stevens *et al.* 1998) and during the N-back tasks (Cattell *et al.* 1998; Carter *et al.* 1998). In contrast, patients exhibited relatively increased activation in the PFC during performance of a modified

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version of the Sternberg Item Recognition Paradigm (Manoach *et al.* 1999, 2000). In yet two other studies, schizophrenia patients failed to activate PFC, but only in the face of diminished performance of a graded memory task (Fletcher *et al.* 1998) and the N-back task (Perlstein *et al.* 2001). Manoach (2003) has offered a plausible explanation for these discrepant findings. In healthy volunteers increases in the working-memory load are accompanied by the increases in the PFC activation (Rypma & D'Esposito, 1999), however, further enhancement of working-memory load is usually associated with a decline in the individual's capacity to process information and reduction of the PFC function (Callicott *et al.* 1999). Manoach (2003) has proposed that this inverted U-shaped function is shifted to the left in schizophrenia patients, such that the increase, plateau and eventual decrease in PFC activation can be observed with lower working-memory-load conditions than in healthy individuals. The results obtained in our recent longitudinal study of first-episode schizophrenia patients during performance of the N-back task support and extend this hypothesis (Mendrek *et al.* in press). Specifically, we observed that in addition to the leftward shift there might exist a downward shift in prefrontal function. Moreover, we found that while left dorsolateral prefrontal cortex (DLPFC), left thalamus, and right cerebellum remained disturbed in patients, the dysfunction of the right DLPFC, right thalamus, left cerebellum and cingulate gyrus normalized with antipsychotic treatment and significant reduction in symptomatology (Mendrek *et al.* in press).

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The purpose of the present study was to evaluate the functional neuroanatomy in clinically remitted, relatively highly functioning schizophrenia patients during performance of the N-back task and determine whether the anomalous activation in the DLPFC, thalamus and cerebellum observed in the acutely psychotic and partially remitted patients, will be also present in this group.

METHOD

Subjects

Sixteen clinically stable outpatients diagnosed with schizophrenia according to DSM-IV

criteria (APA, 1994), underwent the scanning procedure. The data obtained in four patients had to be discarded from the final analysis due to their excessive movement in the scanner or performance below the predetermined acceptable level of accuracy (70%). Out of the remaining 12, all of which were included in the final analysis (nine males; mean age = 28.75 years, s.d. = 9.13 years), eight patients were receiving treatment with olanzapine (mean daily dose 15 mg, s.d. = 5 mg), while four were on risperidone (mean daily dose 2.75 mg, s.d. = 0.9 mg); one patient was receiving both drugs. In addition to an interview and review of case-file material for the purpose of diagnosis, all patients were assessed with the Signs and Symptoms of Psychotic Illness (SSPI) scale, which measures severity of 20 signs and symptoms of acute and chronic psychotic illness. A score of 18 (s.d. = 7) is typical of acute schizophrenia (Liddle *et al.* 2002). The group of patients in the present study obtained a mean score of 8.58 (s.d. = 7.45) [in comparison, in our study of first-episode schizophrenia patients, the group of acutely psychotic patients obtained a mean score of 19.85 (s.d. = 10.72) during the first assessment with SSPI and a mean score of 13.0 (s.d. = 10.78) during the second assessment, 6–8 weeks later, while in partially remitted state]. The relatively low symptoms scores reflect the fact that the patients were in a clinically stable phase of the illness. The group of 12 healthy control subjects was matched with the group of patients on age (mean age = 27.75 years, s.d. = 7.48 years), gender, parental socioeconomic status, and estimated pre-morbid and current IQ. The parental socio-economic status was assessed using the Hollingshead criteria for parental social position (Hollingshead & Redlich, 1958), while the estimated pre-morbid and current IQ were measured using the National Adult Reading Test (NART; Sharpe & O'Carol, 1991) and the Quick test (Ammons & Ammons, 1962) respectively. The healthy subjects had no current or past psychotic illness and no psychotic illness in a first-degree relative. All participants were right handed according to the Annett Handedness scale (Annett, 1970). All participants gave written consent after the experimental details were explained to them.

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N-back procedure and behavioral data analysis

The version of the N-back task employed in the present study was based on that used previously in neuroimaging investigations of working memory (e.g. Awh *et al.* 1996; Cohen *et al.* 1997; Jonides *et al.* 1997). The task consisted of two 7-min runs of alternating 30-s periods of 0-back and 2-back conditions with 20-s periods of rest (the subjects participating in the pilot study performed the test in a single 10-min run). Stimuli were presented visually, one at a time for the duration of 250 ms and inter-stimulus interval of 2 s. During the 0-back condition participants saw the instruction 'Press for X' and were required to press the button with their right index finger anytime they saw an 'X' appearing in the sequence of letters. In the 2-back condition they saw instruction 'Press for 2-back' and had to press the button anytime they saw a letter that was identical to one presented two trials back. Both conditions involved similar sensory processing of information and a similar amount of motor activity. Before scanning, subjects were given full instructions and a practice session, which they performed until reaching 70% performance accuracy. Despite successful practice, two patients did not reach the required 70% performance accuracy in the 2-back task during the scanning session and their data were discarded from the final analysis.

The behavioral data were analyzed using separate, between-within repeated measures, condition (0-back, 2-back) \times group (patients, controls) ANOVAs on the performance accuracy and on the reaction-time data. The errors of omission were defined as a failure to respond to the target stimulus within 1500 ms of stimulus onset, while the errors of commission were defined as a response to a non-target stimulus within the same time-frame.

Neuroimaging procedure and analysis

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The functional images acquired in each run were reconstructed off-line and subsequently realigned, motion corrected and normalized into the MRI template and stereotactic space (Talairach & Tournoux, 1988) using statistical parametric mapping software (SPM99; Wellcome Department of Cognitive Neurology). Two patients moved their head excessively while in the scanner and, therefore, their data were discarded from the final analysis. The motion estimates for the remaining participants did not exceed 2 mm or 2° and there were no significant differences between the groups. The realigned and normalized images were smoothed with an 8-mm full-width at half-maximum Gaussian filter.

The statistical analyses were performed in two stages. In the first stage all participants were analyzed using a fixed-effects model. In the computation of this analysis, the observed time-courses of image intensities were temporally filtered to remove noise associated with low-frequency confounds such as respiration. In addition, each type of epoch (i.e. 2-back, 0-back, and Rest) was modeled by a box-car waveform with a temporal delay of 6 s to account for the relatively slow onset of the hemodynamic response. Because the interpretations of comparisons with rest are uncertain due to inherited uncontrollability and heterogeneity of that state in individual subjects, we compared the magnitude of activation during performance of the 2-back with that during the 0-back condition, throughout the analysis. In the second stage, the single image for each participant was created based on the '2-back/0-back' contrast. These contrast images were entered into a second-level random-effects analyses. The groups of patients and controls were analyzed separately using one-sample *t* tests to examine the pattern of cerebral activity during performance of the 2-back *versus* 0-back condition. The significant results of individual groups were reported at the voxel level as well as at the cluster level, corrected for multiple comparisons. Cluster level significance refers to the probability of obtaining a cluster of supra-threshold voxels as extensive as the observed cluster, taking account of the value of the peak *z* value in the cluster. This was computed following the procedure described by Friston *et al.* (1994) as implemented in SPM99. Then, any potential

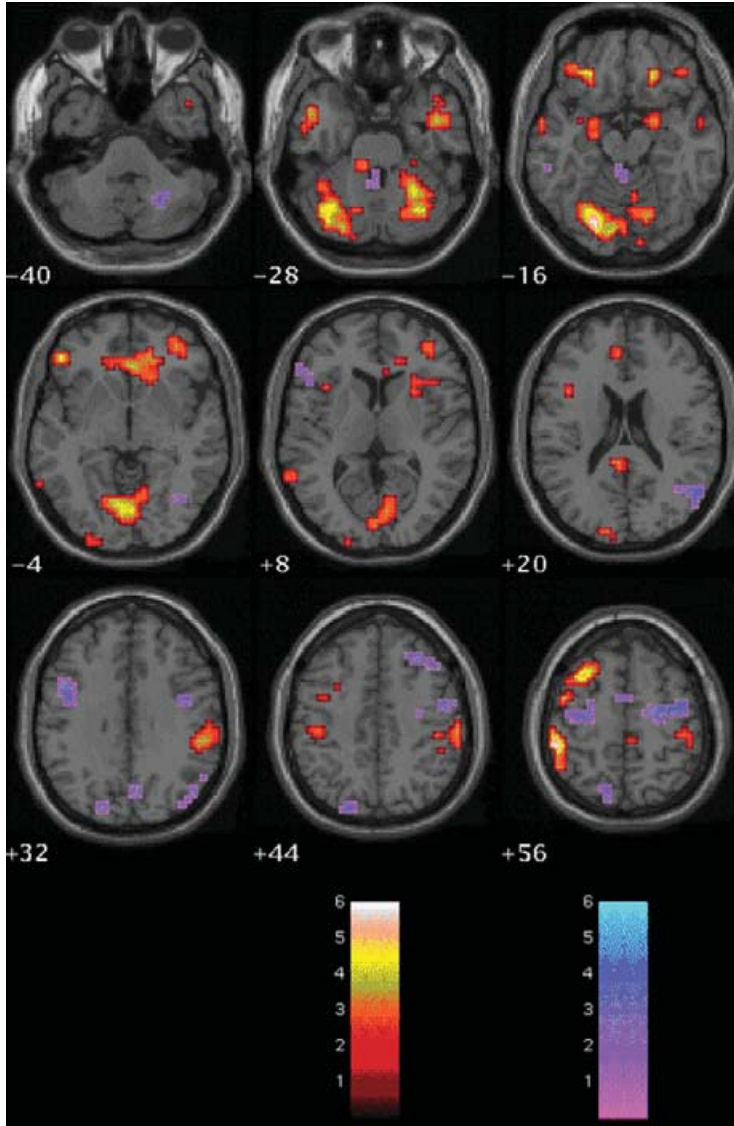


FIG. 1. Illustration of group \times condition interaction during performance of the 2-back *versus* 0-back condition with the relative underactivation of patients *versus* controls depicted in blue and relative overactivation depicted in yellow. The areas of activation reach threshold at $p \leq 0.001$, uncorrected. Colored scales reflect z scores.

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differences between the two groups were explored using a two-sample t test. Despite the advantage of generalizability, when a random-effects analysis is combined with a stringent correction for multiple comparisons that is required when thousands of voxels are examined, there is a serious risk of type II error, unless a very large number of subjects is studied. Therefore, to reduce the risk of type II error

in detecting any potential changes in cerebral activation between the groups, we tested only a restricted set of loci. In accord with our goal of testing the hypothesis that patients would show significant abnormality at the sites where we had observed persistent abnormality in our longitudinal study of first-episode patients, but not at the sites where the first-episode cases had exhibited transient abnormality, we selected

Table 1. *The Talairach coordinates of maximally activated voxels during performance of the 2-back versus 0-back condition by 11 healthy volunteers in the pilot study ($p \leq 0.05$, corrected for multiple comparisons in the entire brain volume). These loci formed a basis for six ROIs (spherical volumes with 12-mm radius) used in the between-group data analysis*

Region	Talairach coordinates		
	x	y	z
'2-back' versus '0-back'			
AQ10 (1) L middle frontal G (BA 46)	-48	34	20
AQ10 (2) R middle frontal G (BA 46)	52	34	20
(3) L cerebellum	-38	-60	-25
(4) R cerebellum	34	-60	-30
(5) L thalamus	-12	-6	10
(6) R thalamus	16	-4	10

regions of interest (ROIs) in which we had found either persistent or transient abnormality in the study of first-episode patients (Mendrek *et al.* in press). In the first-episode study we had tested for differences between patients and controls in 10 ROIs that had initially been identified as sites engaged during working-memory performance in a previous pilot study of healthy individuals. We had found significant abnormality in the first-episode patients when acutely ill, in six of these ROIs. These six ROIs consisted of spherical regions (with 12-mm radius) located bilaterally in the DLPFC, thalamus, and cerebellum, centered on the voxels of maximal activation during performance of the 2-back *versus* 0-back task by healthy volunteers in the pilot study (the exact coordinates of these maximally activated voxels are presented in the Table 2). The abnormality in three of these ROIs (left DLPFC, left thalamus, right cerebellum) had persisted after treatment. In the current study of stable patients we examined the six ROIs, to test the hypothesis that stable patients would exhibit significant abnormality in left DLPFC, left thalamus and right cerebellum. In testing for the significance of the differences between the groups in these regions, we applied small-volume correction procedure as implemented in SPM99 (Poline *et al.* 1997; Worsley *et al.* 2002). In order to avoid the risk of artifactual suppression of local cerebral activity that can be introduced by the use of global normalization to adjust for variations in global

signal intensity (Andersson, 1997; Aguirre *et al.* 1998), no global normalization was performed.

RESULTS

Behavioral data

Two-way ANOVA for the errors of omission committed by schizophrenia patients and matched control subjects revealed that all participants committed more errors of omission during the 2-back than during 0-back condition [main effect of condition, $F(1, 22) = 49.1$, $p < 0.001$]. However, neither interaction [group \times condition, $F(1, 22) = 0.31$, $p < 0.68$], nor main effect of group [$F(1, 22) = 0.41$, $p < 0.53$] was significant, indicating that the two groups achieved a similar level of accuracy. The separate ANOVA for the errors of commission revealed no significant findings [main effect of group, $F(1, 22) = 1.41$, $p < 0.24$; main effect of condition, $F(1, 22) = 0.05$, $p < 0.83$; group \times condition interaction, $F(1, 22) = 0.05$, $p < 0.83$]. Finally, the two-way ANOVA of the reaction time showed that it took longer to respond accurately during the 2-back than during the 0-back condition [main effect of condition, $F(1, 22) = 56.71$, $p < 0.001$] and that schizophrenia patients were slower at responding in both conditions [main effect of group, $F(1, 22) = 5.81$, $p < 0.03$] than were controls. No significant interaction was found [$F(1, 22) = 2.32$, $p < 0.14$].

Neuroimaging data

The separate within-group random-effects analyses of schizophrenia patients and healthy control subjects revealed that the two groups exhibited a similar pattern of cerebral activation during performance of the 2-back relative to the 0-back condition. Both groups showed significant activation in widespread areas of bilateral PFC, parietal cortex, cerebellum and thalamus, as well as deactivations in bilateral temporal cortex, medial PFC, and cingulate cortex (Tables 2 and 3). Despite overall similarities, the between-group random-effects analysis in the six ROIs, as well as exploratory search in the entire brain volume, revealed several significant differences between patients and controls. Thus, the comparison in the six ROIs exposed relatively less activation in the region of the left DLPFC and the right cerebellum, together with more activation in the left cerebellum in

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Table 2. Summary of the significant areas of activation and deactivation in healthy control subjects during performance of the 2-back versus 0-back condition, based on random-effects analysis

Region	Talairach coordinates			Local maxima z score	
	x	y	z		
Activations					
Frontal lobes					
AQ10	(1) L middle frontal G (BA 6)	-44	-4	36	5.27**
	(2) R middle frontal G (BA 46)	44	28	24	5.01**
	(3) R middle frontal G (BA 6)	32	-4	60	4.71**
	(4) L middle frontal G (BA 46)	-40	48	20	4.65**
Parietal lobes					
AQ11	(5) R inferior parietal L (BA 40)	40	-56	48	5.92**
	(6) R precuneus (BA 19)	36	-68	40	5.42**
	(7) L precuneus (BA 19)	-32	-72	44	5.33**
	(8) L inferior parietal L (BA 40)	-40	-52	44	4.96**
Deep grey and cerebellum					
AQ10	(9) L cerebellum	-36	-60	-40	4.68**
	(10) R cerebellum	40	-64	-36	4.63**
	(11) R thalamus	4	-16	12	4.48*
	(12) L thalamus	-8	-20	12	4.41*
Deactivations					
Frontal lobes and cingulate gyrus					
AQ1	(1) L medial frontal G	-12	48	-12	4.32*
	(2) L posterior cingulate (BA 23)	-8	-48	20	4.26*
	(3) L anterior cingulate (BA 24)	-4	32	-4	4.19*
Temporal lobes					
AQ1	(4) R superior temporal G (BA 42)	52	-16	8	4.84**
	(5) R middle temporal G (BA 21)	44	12	-40	4.51*
	(6) L fusiform G (BA 20)	-32	-36	-20	4.39*

* $p \leq 0.05$ corrected for entire volume at the cluster level, threshold at $p \leq 0.01$.

** $p \leq 0.05$ corrected for entire volume at the voxel level.

schizophrenia patients compared with healthy control subjects (Table 4). The exploratory whole-brain random-effects analysis added to that list: relative overactivations of the left superior parietal, medial frontal and anterior cingulate cortices (Table 5). The examination of the between-group differences revealed that the relative overactivations in the anterior cingulate cortex and medial PFC were due to less deactivation of these structures in schizophrenic patients than in control subjects during performance of the 2-back versus 0-back condition.

DISCUSSION

The pattern of cerebral activity during performance of the N-back task in clinically stable schizophrenia patients and healthy subjects was consistent with results obtained in the pilot study and in the previous neuroimaging investigations of a working-memory function in normal volunteers. The significant activations in the DLPFC, premotor cortex, parietal cortex

and cerebellum, were reported in majority of previous studies (e.g. D'Esposito *et al.* 1995; Awh *et al.* 1996; Cohen *et al.* 1997; Jonides *et al.* 1997), and relative deactivations in the temporal cortex, cingulate gyrus and medial PFC, during performance of the 2-back versus 0-back condition, were demonstrated in some studies (e.g. Awh *et al.* 1996; Jonides *et al.* 1997).

Although overall schizophrenia patients and healthy control subjects exhibited a similar pattern of cerebral activity during performance of the N-back task, several important differences between the groups became evident. Specifically, the ROI analysis revealed that activation intensity in the region of left DLPFC and right cerebellum was lower, while activation in the left cerebellum was higher in patients relative to control subjects. The exploratory search in the entire brain volume exposed additional overactivity in patients in the left superior parietal, medial prefrontal and anterior cingulate cortices. Thus, schizophrenia patients exhibited a complex disturbance in a widespread network

Table 3. Summary of the significant areas of activation and deactivation in schizophrenia patients during performance of the 2-back versus 0-back condition, based on random-effects analysis

Region	Talairach coordinates			Local maxima z score	
	x	y	z		
Activations					
Frontal lobes					
AQ10	(1) L middle frontal G (BA 46)	-44	24	24	5.56**
	(2) R middle frontal G (BA 46)	40	32	28	5.25**
	(3) R middle frontal G (BA 6)	28	0	52	5.19**
	(4) L middle frontal G (BA 6)	-32	4	52	5.18**
Parietal lobes					
AQ11	(5) R inferior parietal L (BA 40)	44	-44	44	5.69**
	(6) L precuneus (BA 19)	-24	-68	40	5.58**
	(7) R superior parietal L (BA 7)	28	-60	40	5.38**
	(8) L inferior parietal L (BA 40)	-52	-44	52	5.34**
	(9) L middle temporal G (BA 21)	-68	-40	0	4.79**
Deep grey and cerebellum					
	(10) R cerebellum	28	-68	-36	5.42**
	(11) L cerebellum	-36	-64	-36	5.21**
	(12) L thalamus	-16	0	12	4.85**
	(13) R thalamus	8	0	12	4.71*
Deactivations					
Frontal lobes and cingulate gyrus					
	(1) L medial frontal G	-4	48	-12	4.70*
	(2) L posterior cingulate (BA 30)	-8	-56	4	4.02*
Temporal lobes					
	(3) R superior temporal G (BA 13)	40	-28	8	4.69*
	(4) L insula (BA 13)	-40	-28	16	4.45*

* $p \leq 0.05$ corrected for entire volume at the cluster level, threshold at $p \leq 0.01$.** $p \leq 0.05$ corrected for entire volume at the voxel level.

Table 4. The summary of significant differences in six pre-selected ROIs (12-mm radius spheres) between stable schizophrenia patients and control subjects during performance of the 2-back versus 0-back condition, based on random-effects analysis and the small-volume correction in six ROIs (12-mm radius spheres)

Region	Talairach coordinates			z score	p value	
	x	y	z			
Control – Schizophrenia patients (relative underactivations in patients)						
AQ10	(1) R cerebellum	24	-60	-40	3.38	0.03
	(2) L middle frontal G	-52	32	12	3.11	0.06
Schizophrenia – Control subjects (relative overactivations in patients)						
	(3) L cerebellum	-32	-64	-32	4.88	0.001

of brain areas with significantly lower activation in the circumscribed ROI in the left DLPFC and cerebellum, but overall greater activation in several other regions than that observed in controls.

The finding of augmented cerebral activation is consistent with the recent report by Ramsey

and colleagues (2002) who suggested that the inefficiency of neural communication in schizophrenia results in excessive recruitment of neural systems in patients relative to control subjects during comparable performance on cognitive tasks. In the present study performance accuracy did not differ significantly between the

Table 5. The summary of exploratory whole-brain volume search of differences between stable schizophrenia patients and control subjects during performance of the 2-back versus 0-back condition, based on random-effects analysis

Region	Talairach coordinates			z score	Cluster size	
	x	y	z			
Schizophrenia – Control subjects (relative overactivations in patients)						
AQ11	(1) L superior parietal L	–48	–36	60	5.85**	39
	(2) L cerebellum	–24	–76	–20	5.33**	158
AQ10	(3) L medial frontal G	–4	–4	72	4.80**	12
	(4) R anterior cingulate	12	36	–8	4.43*	44
	(5) R cerebellum	32	–68	–28	4.34*	42

* $p \leq 0.05$ corrected for entire volume at the cluster level, threshold at $p \leq 0.01$.

** $p \leq 0.05$ corrected for entire volume at the voxel level.

groups, but patients were slower than control subjects. The increased reaction time during performance of a working-memory task has been proposed to reflect greater difficulty with the task and has been shown to be associated with more extensive activity in the posterior parietal cortex in healthy volunteers (Honey *et al.* 2000). Therefore, present results of enhanced activation in the parietal cortex (and perhaps other areas as well) may reflect patients' increased effort in attaining equivalent levels of performance with healthy participants.

Alternatively, the hypothesis of compensatory overactivity in the patients might be framed in terms of the use of different cognitive strategies, and thus recruitment of alternative neural circuits during performance on the N-back task. Several studies have provided evidence that the PFC is responsible for the central executive and phonological loop component of a working-memory function, while the posterior parietal cortex appears to serve as a phonological storage of information (Paulesu *et al.* 1993; Awh *et al.* 1996; Cohen *et al.* 1997). Thus, the simultaneous underactivation of the PFC and overactivation of the parietal cortex, in patients relative to control subjects, may reflect their diminished reliance on manipulation and rehearsal, and more on a pure storage of information.

The concurrent dysfunction of the PFC and cerebellum found in schizophrenia patients in the present study is consistent with a series of studies exploring brain function during performance of various cognitive tasks. For example, during recall of complex narrative material and

word lists, healthy control subjects activated an extensive network of regions including the PFC, thalamus, and cerebellum, whereas schizophrenia patients failed to activate these regions despite their matched performance (Andreasen *et al.* 1996; Crespo Facorro *et al.* 1999). In two other studies performed by the same group, schizophrenia patients exhibited diminished activation in the PFC and cerebellum relative to controls, during recognition memory for word lists and faces (Paulsen *et al.* 1998; Wiser *et al.* 1998). However, in the present study, together with relative underactivations in the circumscribed region of the right cerebellum, we observed significant overactivation in both the right and left cerebellum, thus complicating a potential conclusion of straightforward support for the 'cognitive dysmetria' theory of schizophrenia (Andreasen, 1999).

In addition to abnormalities in the lateral PFC, parietal cortex and cerebellum, we observed relative overactivation in patients in the medial PFC and the anterior cingulate cortex, due to less deactivation in these regions in schizophrenia patients than in controls during performance of the 2-back *versus* 0-back condition. The observation of cerebral regions with diminished activation during the 2-back condition compared to the 0-back condition is perhaps surprising if it is assumed that performance of the 2-back task engages all of the processes engaged during the 0-back task. It is possible that subjects might engage in additional incidental mental activity during the easier task. For example, in an interesting study, McGuire and colleagues investigated neural circuitry

implicated in processing stimulus-independent thoughts and found that the frequency of these random thoughts was positively correlated with activation in the medial PFC and anterior cingulate (McGuire *et al.* 1996). Thus, the relative underactivations in the medial PFC and anterior cingulate may represent greater frequency of random thoughts during the cognitively less demanding 0-back *versus* 2-back condition. In this case, the relative failure to suppress the cingulate gyrus by stable schizophrenia patients in comparison to control subjects may reflect diminished frequency of random thought during the 0-back *versus* 2-back condition.

The effects of antipsychotic medications on functional neuroanatomy are still poorly understood and only a few studies have currently addressed this problem. For example, Paulus and associates (2002) showed that during the decision-making task patients exhibited less activation in the PFC and temporal cortex, and more activation in the postcentral and parietal cortex than healthy comparison subjects. Moreover, task-related activations in the PFC and parietal cortex were greater in medicated than in unmedicated patients. Honey and colleagues (1999) demonstrated that after switching patients from typical to atypical antipsychotic medication, patients exhibit an increase in prefrontal and parietal activation during performance of a working-memory task. Ramsey and collaborators (2002) reported that in comparison to healthy control subjects, performance-corrected activity was significantly elevated in medication-naive patients but normalized in patients treated with atypical antipsychotic medication. In our recent longitudinal study of first-episode schizophrenia patients treated with atypical antipsychotic agents, we have also observed normalization of the cerebral function during performance of the N-back task (Mendrek *et al.* in press). Thus, although the influence of medication on the pattern of cerebral disturbance in patients relative to controls observed in the present study, cannot be ruled out, the existing literature suggest that atypical antipsychotic agents should have normalized cerebral function, rather than disturbing it further.

Our findings are not only consistent with the large body of evidence indicating prefrontal

malfunction in schizophrenia (Weinberger & Berman, 1996; Manoach, 2004), but indicate that left prefrontal abnormality is a more persistent feature. This suggests a reformulation of the speculation advanced by Flor-Henry (1969) years ago that schizophrenia arises from left temporal abnormality and affective psychosis from right temporal abnormality, with the hypothesis that the persistent features of schizophrenia reflect predominant malfunction of the left cerebral hemisphere and right cerebellum. However, overall, our findings suggest that any such generalization is a simplification of the complex pattern of brain malfunction in schizophrenia. Future studies should elucidate this problem further.

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DECLARATION OF INTEREST

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