Psychological Medicine, 2005, **35**, 1019–1030.
doi:10.1017/S0033291705004393 Printed in the United Kingdom

Functional MRI of visuospatial working memory in schizotypal personality disorder: a region-of-interest analysis

HAROLD W. KOENIGSBERG[1,2]*, MONTE S. BUCHSBAUM[2], BRADLEY R. BUCHSBAUM[3], JASON S. SCHNEIDERMAN[2], CHEUK Y. TANG[2,4], ANTONIA NEW[1,2], MARIANNE GOODMAN[1,2] AND LARRY J. SIEVER[1,2]

[1] *Bronx Veterans Affairs Medical Center, Bronx, NY, USA*; [2] *Department of Psychiatry, Mount Sinai School of Medicine, New York, NY, USA*; [3] *National Institutes of Health, Bethesda, MD, USA*; [4] *Department of Radiology, Mount Sinai School of Medicine, New York, NY, USA*

ABSTRACT

Background. Functional MRI studies have begun to identify neural networks implicated in visuospatial working memory in healthy volunteers and patients with schizophrenia. The study of schizotypal personality disorder (SPD) provides regional analysis in unmedicated patients in the schizophrenia spectrum.

Method. Unmedicated patients with SPD by DSM-IV criteria and normal controls were assessed with fMRI while performing a visuospatial working-memory task. It required the subjects to retain the location of three dots located on the circumference of an imaginary circle and then respond to a query display in which one dot was presented and the subject required to press a button to indicate whether the probe dot location was previously displayed. Subject groups did not differ significantly in spatial memory scores. The exact Talairach and Tournoux coordinates of brain areas previously reported to show activation with spatial memory tasks were assessed.

Results. The majority of these locations showed BOLD response activation significantly less in patients during the memory retention period, including the left ventral prefrontal cortex, superior frontal gyrus, intraparietal cortex and posterior inferior gyrus. Regions in the right middle prefrontal and prestriate cortex showed greater activation at a trend level for patients with SPD than for normal controls. In addition, we replicated the findings of increased activation with the task in healthy volunteers in the premotor areas, ventral prefrontal cortex and parietal cortex.

Conclusions. SPD patients show decreased activation compared to healthy volunteers in key frontal regions and we also provided a partial replication of findings reported in healthy subjects.

INTRODUCTION

Cognitive deficits within the schizophrenia spectrum account for much of the functional impairment seen in these disorders. An important aspect of the cognitive deficit is impairment in working memory, the capacity to maintain information in temporary storage for immediate manipulation and use. Working memory is significantly compromised in both schizotypal personality disorder (SPD) (Park *et al.* 1995; Park & McTigue, 1997; Roitman *et al.* 2000; Siever *et al.* 2002) and in schizophrenia (Fleming *et al.* 1997; Keefe *et al.* 1997; Park *et al.* 1999), but more severely in schizophrenia than in SPD.

SPD shares many features in common with schizophrenia including family history, psychophysiology, phenomenology, and some neuroanatomical features (Siever *et al.* 2002).

* Address for correspondence: Dr Harold W. Koenigsberg, Bronx Veterans Affairs Medical Center, 130 West Kingsbridge Road, Bronx NY 1046, USA.
(Email: harold.koenigsberg@med.va.gov)

However while SPD patients do not show the classical psychotic symptoms of hallucinations or delusions, they do show more modest cognitive impairment, intermediate between schizophrenic patients and normal controls. Studies of SPD patients allow investigation of neurocognitive processes in the schizophrenia spectrum while minimizing such confounds as exposure to neuroleptic medication, histories of institutionalization, poor nutrition or other biomedical artifacts of severe mental illness encountered in studies of schizophrenic patients. The absence of positive psychotic symptoms that could interfere with the assessment of cognitive processes may be an additional methodological advantage.

Functional neuroimaging studies have begun to delineate the networks involved in spatial working memory in healthy subjects, identifying increased activity in the ventral prefrontal cortex [Brodmann area (BA) 44/45/47], the supplementary motor area (BA 6), the premotor area (BA 6), the dorsolateral prefrontal cortex (BA 9/46), and various parietal regions (BA 40/19/7) (Jonides *et al.* 1993; McCarthy *et al.* 1994, and see D'Esposito *et al.* 1998 for a review).

In schizophrenic patients, PET, SPECT and fMRI studies of working memory have been carried out using such tasks as the Wisconsin Card Sort task (WCST) (Weinberger *et al.* 1988), the 'N-back' memory task (Callicott *et al.* 1998), the Sternberg Item Recognition Paradigm (Manoach *et al.* 1999) and word-list learning (Fletcher *et al.* 1998), which call into play different forms of working memory. Reduced frontal lobe activity in comparison to normal controls has been widely observed in patients with schizophrenia, as reviewed elsewhere (Andreasen *et al.* 1997; Buchsbaum & Hazlett, 1998). This has also been shown for tasks involving verbal memory (Buchsbaum *et al.* 1999; Hofer *et al.* 2003*a*, *b*; Kumari *et al.* 2003). In a study with the N-back working-memory task, BA 9, 10, 44, 46 and 47 showed decreases in patients and BA 6, 8 and parts of 10 and 46 showed patients more active than normal (Callicott *et al.* 2003).

To date two functional neuroimaging studies of SPD patients employing a working-memory task have implicated dysfunction in the frontal lobe. The first, compared SPD patients and healthy control (HC) subjects as they carried out the WCST, a task that involves object working memory and executive function (Buchsbaum *et al.* 1997). Normal patients showed more activation in the precentral gyrus, while SPD patients showed greater activity in the middle frontal gyrus. The second study compared regional metabolic activity between SPD patients, schizophrenic patients, and healthy volunteers during a task involving verbal working memory (Buchsbaum *et al.* 2002). Patients with schizophrenia showed less activation than HC subjects or SPD patients in BA 9 and 46. In BA 10, SPD subjects showed the greatest activation, schizophrenia patients less activation and HC subjects least activation.

The present study examines regional activation in SPD and HC subjects as they carry out a spatial working-memory task adapted from the task of Keefe *et al.* (1997). This task demonstrates poorer spatial memory in SPD than normal controls (Roitman *et al.* 2000) and has demonstrated test–retest reliability (Bollini *et al.* 2000). Our study employs an event-related design to aid in differentiating activation during the maintenance phase of working memory from that during manipulation, retrieval and responding. To avoid the potential confound of differing levels of performance between groups, we developed a task at which SPD and HC subjects performed comparably following the recommendations of other groups (e.g. Weinberger & Berman, 1996). We carried out a region-of-interest (ROI) analysis examining regions that other investigators reported to be activated during working-memory tasks. This hypothesis-driven approach minimizes Type II error and permits direct comparison with other fMRI studies. Tests of replicability between studies are particularly important in this area because of the great variability in locations of activation reported in different studies (D'Esposito *et al.* 1998; Manoach, 2003).

We hypothesize that, while performing the spatial working-memory task, SPD patients will show decreased activation compared to HC subjects during the memory maintenance period in those regions identified in the literature as part of the spatial working-memory network. In addition, we will test whether regions identified in the literature as implicated in working memory in healthy volunteers are activated in our sample of healthy subjects.

METHOD

Subjects

Subjects were six medication-free SPD patients and seven HC subjects between the ages of 20 and 50 years. The SPD patients met DSM-IV criteria for SPD and did not meet criteria for past or present schizophrenic disorder, bipolar I disorder, schizoaffective disorder, substance dependence, organic mental syndromes, head trauma, CNS neurological disease, or seizure disorder, or, within 6 months prior to entry, substance abuse disorder. HC subjects had no DSM-IV Axis-I or Axis-II disorder and no first-degree relatives with a DSM-IV Axis-I disorder. Subjects were free of psychotropic medication for 2 weeks prior to the study and had no significant medical illness.

For diagnostic assessments we used the Schedule for Affective Disorders and Schizophrenia (SADS) and the Structured Interview for Personality Disorders (SID-P), administered by experienced interviewers (with an inter-rater reliability kappa of 0·73 for diagnosing SPD and 0·98 for schizophrenia).

Task

The visuospatial working-memory task, adapted from the paper-and-pencil dot test of known reliability (Bollini *et al*. 2000) and modeled on the functional imaging task of Jonides *et al*. (1993), requires the subject to remember the locations of three dots over a 29·8 s delay period and then to respond to a query display in which one dot is presented and the subject is required to press a button to indicate whether that dot location had appeared in the immediately preceding three-dot pattern (Fig. 1).

BOLD fMRI images (event-related design) were acquired as the subjects performed 30 trials, 15 memory trials and 15 control trials grouped in five blocks of six trials each, with the control and memory trials alternating in each block. Subjects viewed the task images back-projected onto a screen located in front of the magnet bore.

Imaging methods

Thirty BOLD images of the whole brain were obtained at 2-s intervals over the 60-s duration of each trial (GE Signa LX 8.2.5 1.5 T system, real-time gradient echo EPI sequence: TR = 2 s, TE = 40 ms, flip angle = 90°, FOV = 23 cm, matrix = 128 × 128, thickness = 5 mm, skip = 2·5 mm). Fourteen transverse planes covered the whole brain.

Anatomical images were obtained for co-registration (SPGR sequence; repetition time = 24 ms, echo time = 5 ms, flip angle = 40°), for contiguous 1·2-mm-thick axial slices, with a 256 × 256 pixel matrix in a 23-cm field of view.

Head motion was minimized by means of a pillowed head cradle and a tape restraint across the subject's forehead.

Image processing

BOLD signals were pre-processed by removal of the mean and linear trends, and digital spectral filtering to remove low- and high-frequency values outside the range of the primary blood flow response. Each set of successive fMRI brain images was co-registered in 3D to the first set of each of the 14 slices at time 0 for each trial (AIR 3.08), and subjects whose average transformation over all images was >2 mm were excluded.

ROIs

ROIs were defined a priori on the basis of published reports that identified the Talairach coordinates of regions activated during working-memory tasks in healthy subjects or in patients with schizophrenia (Table 1). Since each of these regions would be a replication of a published result with our independent sample, it was appropriate to apply a $p < 0{\cdot}05$ criterion. It would be unfair to any earlier study to report that we failed to replicate when our independent test reached $p < 0{\cdot}05$. In addition to reducing Type II errors, this approach tests the replicability of findings across imaging studies. Five studies that examined working memory provided the basis for the ROIs. The first (D'Esposito *et al*. 1998) was selected because it presented data synthesized from 24 functional neuroimaging studies of working memory in healthy volunteers. This report provided the mean Talairach coordinates across these studies of the local maxima of activations in the dorsal and ventral prefrontal cortex for spatial working-memory tasks. The second study (Rowe & Passingham, 2001) was selected because it used an event-related fMRI spatial working-memory

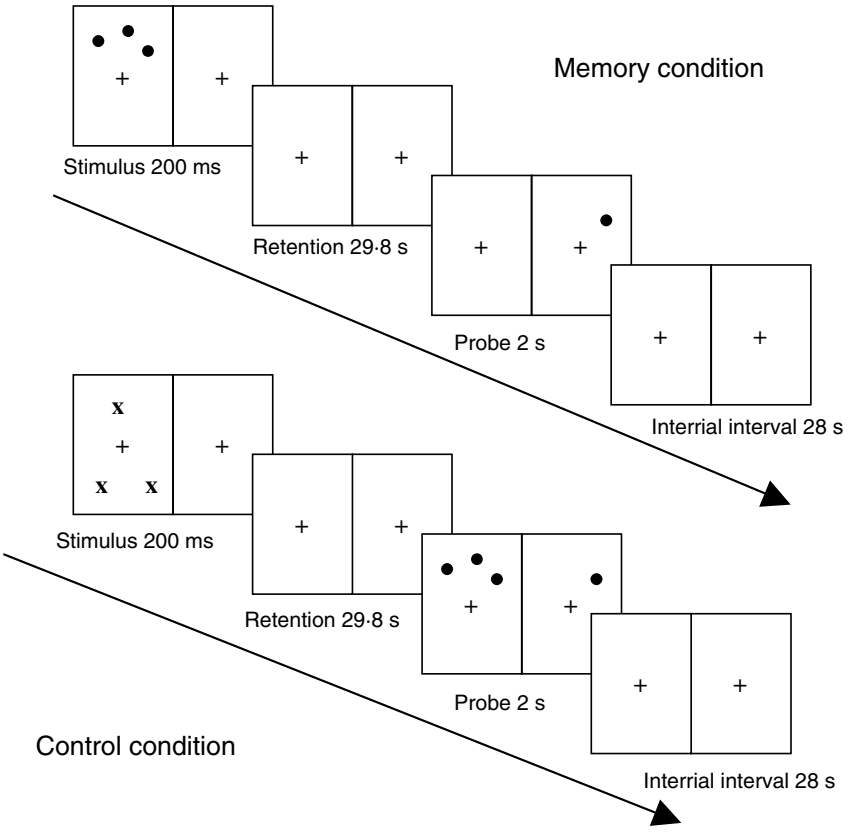

FIG. 1. Schematic diagram of visuospatial task. For each trial the three-dot stimulus is presented for 200 ms and is followed by a fixation cross for the duration of the 29·8 s memory retention (maintenance) period. This is followed by a query display, presented for 2 s, and then a 28-s inter-trial interval. In the control condition, subjects are presented with an initial stimulus pattern, a pattern of 3 x's, comparable in visual complexity to the experimental stimulus, but which need not be remembered to correctly respond to the query. This is because when the query screen appears in the control condition, the subject is shown the three-dot stimulus pattern in a panel alongside the panel with the probe dot. As in the experimental trial, the initial stimulus appears for 200 ms, is followed by a 29·8 s fixation cross, and a 2 s presentation of the query screen. The control task is comparable to the experimental task in visual stimulus complexity, timing, decision-making requirements and motor response, and differs only in the absence of a working-memory requirement. Each memory and control trial has a duration of 60 s, including the interstimulus interval.

design to distinguish between maintenance and selection/retrieval processes. The third study was a PET study (Jonides *et al.* 1993) which used a working- memory task similar to ours. The fourth study (Manoach *et al.* 2000), which employed a verbal working-memory task, was selected because it included a group of patients with schizophrenia as well as HC subjects. The fifth (Kindermann *et al.* 2004), a spatial working-memory fMRI study, compared schizophrenic patients to HC subjects. We hypothesized that in each of the locations reported in these studies to be activated during a working-memory task, we would find greater maintenance period activation in healthy volunteers than in SPD patients, in the memory condition compared to the control condition.

We defined ROIs ($8\ \text{mm} \times 8\ \text{mm} \times 7{\cdot}5\ \text{mm}$) centered at the Talairach locations specified in the cited papers. These regions were applied proportionately to each individual structural MRI and the BOLD value assessed on the co-registered BOLD image. Co-registration was carried out using a six-parameter affine transformation (x, y, z translation and rotation in each plane). In some cases, Talairach coordinates for cortical surface areas would fall outside an individual's MRI indicated by zero activation. In these instances we translated the center of the ROI slightly along a radial path to

the center of the slice (Talairach x = y = 0) so that the entire volume was contained within the brain. ROI boxes that were above the brain in the *z*-plane were moved down 7·5 mm. Boxes that fell in the longitudinal fissure were divided into two separate boxes, one right and left of the midline by 8 mm. We excluded those few regions in subjects in which the ROI continued to partially lie outside of the brain even after these spatial adjustments.

Data analysis

For each ROI we obtained the mean activation of all voxels within the region at each of the 30 time-series points for each trial. To test for BOLD activation in response to the visual stimulation, we examined the main effect of time in a repeated-measures analysis of variance (ANOVA) in all the ROIs cited in the literature. To test for spatial working-memory activation in the HC subjects in those regions indicated in the literature to be involved in spatial working memory, a repeated-measures ANOVA was carried out at each ROI with time, condition (memory *versus* control), and task (retention *versus* retrieval/response) as the within-subjects measures. For the comparison between groups, a repeated-measures ANOVA was carried out at each ROI with time, condition, and task as the within-subjects measures and group (HC *versus* SPD) as the between-subjects variable. An additional exploratory comparison added hemisphere as an additional repeated measure for those regions which had results reported for both hemispheres.

RESULTS

Data from two of the seven HC subjects were not included in the analysis because of a damaged data file in one instance and extreme outlier BOLD values in the other. Table 2 displays characteristics of the included subjects. The two groups were similar in age and gender. The SPD subjects had less education than the HC subjects. The split-half reliability (Spearman–Brown) for the working-memory task was 0·83 ($p < 0·005$) in the control condition and 0·40 ($p =$ N.S.) in the memory condition. Both SPD and HC subjects performed better (a higher percentage of correct responses) on the control task than on the memory task and the HC subjects performed better on each task than the SPD subjects, although the differences did not reach significance (memory task: 54·2 ± 15·0% SPD *versus* 63·7 ± 5·5% HC; control task: 66·7 ± 18·8% SPD *versus* 77·2 ± 12·0% HC). The groups did not differ significantly on mean performance in a MANOVA with control and memory task scores when age ($F = 2·47$, df = 2, 7, $p = 0·15$) and when age and educational level were entered as covariates ($F = 2·25$, df = 2, 6, $p = 0·19$).

The results for all the ROIs examined are presented in Table 1. For 35 of the 79 ROIs examined, there was a significant main effect of time, indicating a time-varying BOLD activation in these regions in response to the performance of the task.

Regional activation in healthy volunteers

During the memory maintenance period, there was significantly greater activation in the memory task than the control task in right ventral prefrontal cortex (BA 44/45/47), right and left lateral premotor areas (BA 6), right inferior frontal gyrus, left posterior parietal cortex (BA 19/40/7), left intraparietal cortex, left medial parietal cortex (precuneus), right inferior parietal cortex, right prestriate cortex, and right and left superior parietal lobule/intraparietal sulcus (Table 1). In the left superior temporal gyrus, greater activation was found during the memory task than during the control task in the retrieval/response period (Table 1). Representative time series are shown in Fig. 2.

Regional activation in SPD patients compared to healthy volunteers

To determine whether the SPD patients compared to healthy volunteers showed different levels of activation in the ROIs, we examined time × condition × task × diagnosis interactions (see Table 1). During the maintenance period in the memory condition, the SPD patients showed significantly decreased activation compared to the HC subjects in the left ventral prefrontal cortex (BA 44/45/47) ('A' in Table 1, Fig. 4), the left superior frontal gyrus (BA 10) ('C' in Table 1 and Fig. 4), the left intraparietal cortex ('B' in Table 1, Fig. 4), and the left posterior inferior frontal gyrus (BA 44) ('D' in Table 1, Fig. 4) and decreased activation at a trend level in the left lateral premotor cortex (BA 6), and the left

Table 1. *BOLD activation at reported regions of interest during visuospatial working memory task*

Regions of interest (author/region)	Talairach coord.			Repeated-measures ANOVA: All subjects Time			Patients *v.* controls Cond × Task × Time × Diag		Healthy controls only Cond × Task × Time		
	x	y	z	*F*	df	*p*	*F*	*p*	*F*	*p*	df
D'Esposito *et al.* (1998)											
Dorsal prefrontal cortex (9/46) – R	34	34	26	3·44	13, 117	**0·000**	1·351	0·194	1·214	0·296	13, 52
Dorsal prefrontal cortex (9/46) – L	−38	37	24	1·01	13, 91	0·453	0·419	0·959	1·010	0·461	13, 39
Ventral prefrontal cortex (44/45/47) – R	37	19	−4	1·89	13, 117	0·038	1·136	0·337	2·049	**0·034**	13, 52
Ventral prefrontal cortex (44/45/47) – L [A]	−38	19	−3	12·27	13, 117	**0·000**	1·927	**0·034**	1·398	0·192	13, 52
Lateral premotor (6) – R	28	−1	48	1·23	13, 117	0·266	0·081	1·000	2·701	**0·006**	13, 52
Lateral premotor (6) – L	−26	−3	52	2·44	13, 117	**0·006**	1·735	0·062	2·732	**0·005**	13, 52
Supplementary motor area (6) – R	5	−11	60	1·23	13, 117	0·266	0·081	1·000	0·568	0·868	13, 52
Posterior parietal cortex (19/40/7) – R	28	−57	43	12·38	13, 117	**0·000**	0·745	0·716	1·149	0·342	13, 52
Posterior parietal cortex (19/40/7) – L	−19	−59	44	2·18	13, 117	**0·015**	0·582	0·865	2·519	**0·009**	13, 52
Rowe & Passingham (2001)											
Superior frontal sulcus (8) – R	28	8	52	0·83	13, 117	0·629	0·461	0·942	0·917	0·543	13, 52
Superior frontal sulcus (8) – L	−18	0	48	3·35	13, 117	**0·000**	0·343	0·983	0·714	0·742	13, 52
Intraparietal cortex – R	20	−64	56	1·52	13, 117	0·119	0·172	0·999	0·443	0·945	13, 52
Intraparietal cortex – L [B]	−18	−70	54	2·44	13, 104	**0·006**	2·162	**0·016**	2·714	**0·005**	13, 52
Precentral gyrus – L	−42	3	38	2·95	13, 117	**0·001**	1·762	0·057	1·548	0·132	13, 52
Area 9/46 R	30	10	46	0·75	13, 117	0·710	0·627	0·827	0·251	0·996	13, 52
Area 9/46 L	−24	10	50	0·42	13, 104	0·960	1·360	0·192	0·578	0·856	13, 39
Middle frontal gyrus (46) – R [E]	35	31	40	0·69	13, 117	0·768	1·780	0·054	0·788	0·669	13, 52
Middle frontal gyrus (46) – L	−40	26	18	5·79	13, 117	**0·000**	0·679	0·780	0·690	0·764	13, 52
Inferior frontal gyrus – R	48	14	12	1·95	13, 117	**0·032**	0·817	0·641	2·179	**0·024**	13, 52
Inferior frontal gyrus – L	−40	8	24	9·35	13, 117	**0·000**	1·183	0·300	1·135	0·353	13, 52
Orbitofrontal prefrontal cortex – R	34	24	−12	1·44	13, 117	0·151	1·224	0·271	0·988	0·476	13, 52
Orbitofrontal prefrontal cortex – L	−32	24	−13	1·80	13, 117	0·051	0·558	0·882	1·011	0·455	13, 52
Paracingulate cortex – R	8	24	42	0·09	13, 104	1·000	0·639	0·816	0·699	0·752	13, 52
Paracingulate cortex – L	−8	24	42	0·16	13, 117	1·000	0·699	0·761	1·359	0·211	13, 52
Medial parietal (precuneus) – R	4	−66	44	7·24	13, 117	**0·000**	1·505	0·126	0·709	0·746	13, 52
Medial parietal (precuneus) – L	−10	−70	54	2·13	13, 117	**0·017**	1·258	0·249	2·279	**0·018**	13, 52
Inferior parietal cortex – R	48	−36	42	2·78	13, 117	**0·002**	0·749	0·712	2·204	**0·022**	13, 52
Prestriate cortex – R [F]	16	−94	2	2·89	13, 117	**0·001**	1·790	0·052	2·373	**0·014**	13, 52
Prestriate cortex – L	−10	−100	0	6·15	13, 117	**0·000**	0·168	1·000	0·405	0·962	13, 52
Manoach *et al.* (2000)											
Dorsolateral prefrontal cortex (9/46) – R	36	35	28	3·39	13, 117	**0·000**	0·578	0·867	0·538	0·889	13, 52
Dorsolateral prefrontal cortex (9/46) – L	−35	22	34	2·27	13, 117	**0·011**	0·990	0·465	0·804	0·654	13, 52
Supplementary motor area (6)	0	9	28	25·06	13, 117	**0·000**	0·248	0·996	0·743	0·714	13, 52
Lateral premotor (6) – R	6	2	54	0·79	13, 65	0·538	0·587	0·855	0·964	0·508	13, 26
Lateral premotor (6) – L	−40	0	37	4·25	13, 117	**0·000**	1·178	0·304	0·813	0·644	13, 52
Superior parietal lobule/IP sulcus (7) – R	37	−63	43	10·60	13, 117	**0·000**	1·458	0·144	2·222	**0·021**	13, 52
Superior parietal lobule/IP sulcus (7) – L	−28	−66	43	6·28	13, 117	**0·000**	0·609	0·842	2·729	**0·005**	13, 52
Insula (45) – R	37	21	15	3·95	13, 117	**0·000**	0·161	1·000	1·200	0·306	13, 52
Insula (45) – L	−28	21	12	1·51	13, 117	0·123	0·334	0·985	0·647	0·803	13, 52
Superior frontal gyrus (10) – L [C]	−13	50	34	0·81	13, 104	0·650	1·868	**0·042**	0·462	0·936	13, 52
Middle frontal gyrus (8) – L	−36	9	43	1·18	13, 117	0·306	0·785	0·675	0·760	0·697	13, 52
Ant. inferior frontal gyrus (47) – R	25	39	−6	0·89	13, 117	0·236	0·720	0·740	0·862	0·595	13, 52
Post. inferior frontal gyrus (9/44) – R	40	12	25	10·38	13, 117	**0·000**	0·867	0·590	1·117	0·366	13, 52
Caudate head – R	15	15	6	1·76	13, 117	0·058	1·500	0·128	1·044	0·426	13, 52
Thalamus – R	12	−3	9						0·529	0·896	13, 52
Thalamus – L	−12	−3	9						0·895	0·564	13, 52
Middle frontal gyrus (10) – R	31	48	0	1·91	13, 117	**0·035**	0·420	0·960	1·517	0·143	13, 52
Middle frontal gyrus (10) – L	−31	46	15	1·19	13, 104	0·300	1·167	0·314	0·981	0·482	13, 52
Lentiform nucleus – L	−28	−18	−3	0·76	13, 117	0·705	0·585	0·862	0·419	0·956	13, 52
Post. inferior frontal gyrus (44) – L [D]	−46	7	21	15·66	13, 117	**0·000**	1·817	**0·048**	1·342	0·220	13, 52
Anterior cingulate (24) – R	3	12	25	11·33	13, 117	**0·000**	0·717	0·743	0·522	0·901	13, 52
Superior temporal gyrus (38) – R	50	12	−3	1·94	13, 117	**0·032**	0·430	0·956	1·341	0·221	13, 52
Posterior cingulate (23) – R	3	−36	25	4·42	13, 117	**0·000**	0·658	0·800	0·459	0·938	13, 52
Inferior temporal gyrus – L	−50	−57	−9	1·29	13, 117	0·228	0·939	0·516	0·983	0·480	13, 52
Dorsolateral prefrontal cortex (9/46) – R	37	30	28	5·80	13, 117	**0·000**	0·991	0·464	0·493	0·919	13, 52
Dorsolateral prefrontal cortex (9/46) – L	−46	27	21						0·635	0·814	13, 52
Supplementary motor area (6) – R	8	15	53	0·81	13, 91	0·649	1·017	0·443	0·739	0·711	13, 26
Supplementary motor area (6) – L	−8	15	53						1·010	0·461	13, 39

Table 1 (*cont.*)

Regions of interest (author/region)	Talairach coord.			Repeated-measures ANOVA: All subjects Time			Patients *v.* controls Cond × Task × Time × Diag		Healthy controls only Cond × Task × Time		
	x	y	z	*F*	df	*p*	*F*	*p*	*F*	*p*	df
Lateral premotor (6) – R	28	0	50	0·42	13, 117	0·961	0·304	0·990	2·108	**0·029**	13, 52
Lateral premotor (6) – L	−25	3	50						0·821	0·636	13, 52
Superior parietal lobule/IP sulcus (7) – R	31	−66	50	10·00	13, 117	**0·000**	0·942	0·513	1·632	0·106	13, 52
Superior parietal lobule/IP sulcus (7) – L	−25	−72	46						2·155	**0·026**	13, 52
Insula (45) – R	31	21	9	1·43	13, 117	0·156	0·658	0·800	0·635	0·814	13, 52
Insula (45) – L	−28	18	6						0·787	0·670	13, 52
Jonides *et al.* (1993)											
Prefrontal cortex (47) – R	35	19	2	1·51	13, 117	0·125	0·972	0·483	0·789	0·668	13, 52
Parietal cortex (40) – R	42	−40	36	4·17	13, 117	**0·000**	0·923	0·532	0·537	0·891	13, 52
Occipital cortex (19) – Visual R	30	−76	31	1·61	13, 117	0·091	0·164	1·000	0·902	0·557	13, 52
Premotor cortex (6)	34	−1	45	2·62	13, 117	**0·003**	0·494	0·924	1·038	0·431	13, 52
Kinderman *et al.* (2004)											
Putamen/Globus pallidus – L	−9	6	−8	0·73	13, 117	0·735	0·913	0·542	1·150	0·342	13, 52
Caudate body/Anterior cingulate – L	−16	6	24	1·42	13, 117	0·159	0·851	0·606	1·185	0·316	13, 52
Inferior parietal lobule (40) – L	−44	−40	45	0·89	13, 117	0·562	1·561	0·106	1·040	0·430	13, 52
Precuneus (7) – R	9	−78	52	1·45	13, 117	0·149	0·900	0·559	1·711	0·086	13, 52
Superior temporal gyrus (22) – L [G]	−65	−40	7	0·89	13, 117	0·563	1·902	**0·036**	2·269	**0·019**	13, 52
Fusiform gyrus (19) – L	−37	−64	−11	0·78	13, 104	0·682	0·350	0·982	0·671	0·778	13, 39
Middle occipital gyrus (18) – R	33	−89	3	1·33	13, 117	0·204	1·235	0·264	1·257	0·269	13, 52
Anterior cerebellum (culmen) – R	12	−54	−4	0·98	13, 104	0·479	0·505	0·917	0·837	0·621	13, 39
Medial frontal gyrus (6) – L	−2	−12	49	1·69	13, 117	0·072	0·891	0·564	0·900	0·558	13, 52
Precentral/postcentral sulcus (4) – L	−33	−22	52	2·83	13, 117	**0·001**	0·749	0·712	0·593	0·848	13, 52
Postcentral gyrus/Inf. parietal (2/40) – R	65	−26	35	0·85	13, 117	0·605	0·707	0·754	1·257	0·269	13, 52
Precentral gyrus (4/6) – L	−30	−22	70	0·73	13, 117	0·731	1·354	0·192	1·294	0·246	13, 52

Bold values indicate statistically significant effect, $p < 0{\cdot}05$.

Table 2. *Demographic characteristics of sample*

Subject	Age (years)	Gender	Education (years)	Handedness
Healthy controls				
1	29	M	20	R
2	30	F	20	R
3	25	F	19	R
4	38	M	14	R
5	28	M	20	R
Mean (±s.d.)	30·0 ± 4·9[a]		18·6 ± 2·6[b]	
SPD subjects				
6	42	M	13	L
7	35	M	12	R
8	24	M	16	R
9	21	F	13	L
10	29	M	16	R
11	48	M	13	R
Mean (±s.d.)	33·0 ± 10·7[a]		13·8 ± 1·7[b]	

[a] $t = 0{\cdot}62$, df = 9, n.s.
[b] $t = 3{\cdot}64$, df = 9, $p = 0{\cdot}005$.

precentral gyrus. The SPD patients showed less memory *versus* control condition activation difference than healthy volunteers during the retention period in the left superior temporal gyrus ('G' in Table 1) and trends for greater activation than HC subjects during the retention period in the right middle frontal gyrus (BA 46) ('E' in Table 1, Fig. 4) and the right prestriate cortex ('F' in Table 1, Fig. 4). A representative time series showed decreased activation in SPD patients compared to HC subjects during the retention period in the memory condition in the left posterior inferior frontal gyrus (BA 44) (Fig. 3). The regions with the key condition × task × time × diagnosis interaction are shown in Fig. 4.

We examined lateralization with a five-way ANOVA with hemisphere × time × condition × task × diagnosis interactions. For the four D'Esposito regions, while there were some interactions (time × hemisphere), no interaction involving condition or diagnosis was significant. For the nine Rowe regions, only the medial parietal region showed a significant hemisphere × condition × time effect ($F = 1{\cdot}90$, df = 13, 117, $p = 0{\cdot}027$) with a greater left hemisphere

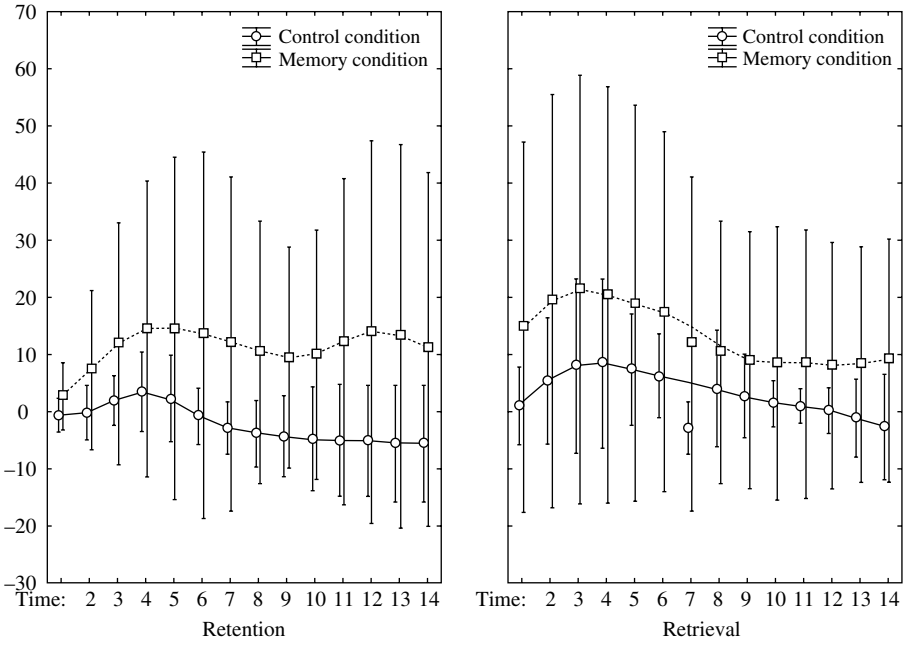

FIG. 2. Repeated-measures ANOVA least squares means of BOLD activation in the left lateral premotor area in healthy control subjects during the retention period and the retreival period in the memory condition and the control condition.

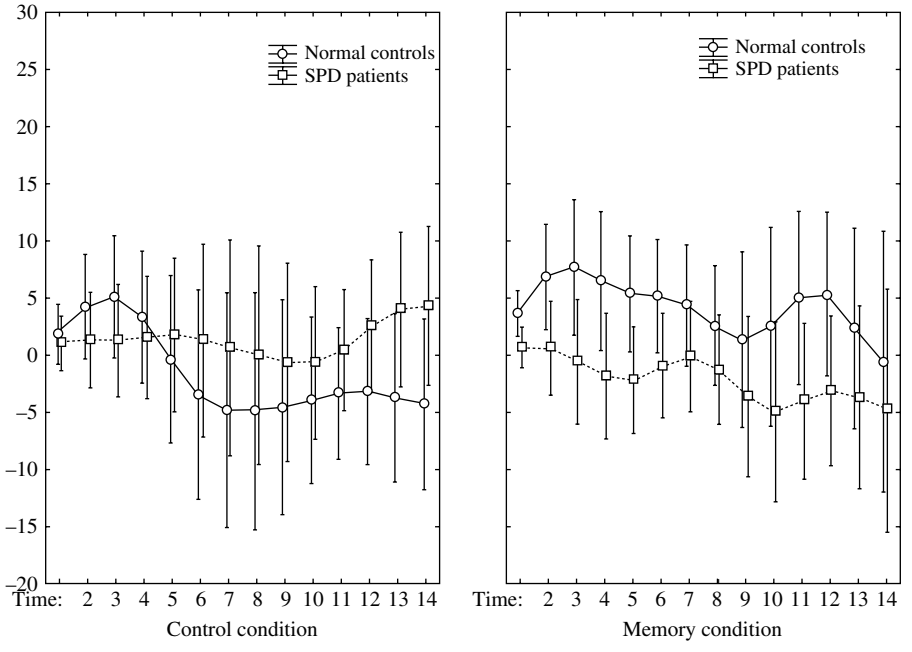

FIG. 3. Repeated-measures ANOVA least squares means of BOLD activation in the left posterior inferior frontal gyrus during the retention period in SPD patients and healthy control subjects for the memory trials and the control trials [$F(13, 117) = 1{\cdot}817$, $p = 0{\cdot}048$].

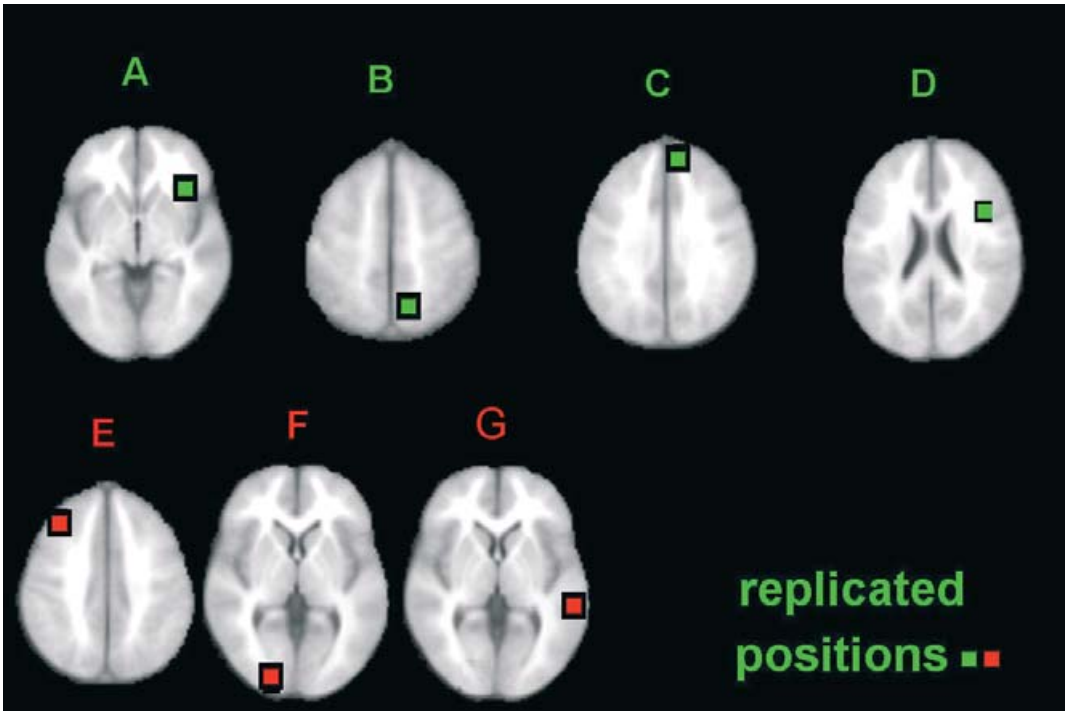

FIG. 4. Talairach locations of replicated regions. Location of regions with condition × task × time × diagnosis in our data analysis which were replicated from other studies (see Table 1). Regions with $p = 0{\cdot}05$ were chosen for illustration ($E = 0{\cdot}054$). The letters A–G refer to the locations flagged in Table 1. Green indicates regions with less activity in SPD subjects compared to controls; red indicates regions in which SPD subjects show greater activity than controls.

effect. For the 11 Manoch regions, only the middle frontal gyrus showed a significant hemisphere × condition × time effect ($F = 2{\cdot}90$, df = 13, 117, $p = 0{\cdot}001$) greater on the right in the memory condition and greater on the left in the control condition.

DISCUSSION

A strength of the present study is its event-related design, which allows us to select the maintenance (and encoding) phases of the working-memory task, apart from manipulation, retrieval and response selection. In contrast, block design fMRI, PET and SPECT measure activation associated with the sum total of all of these components. We have confirmed a number of findings reported in healthy volunteers and demonstrated a pattern of decreased activation in SPD compared to HC subjects in regions shown to be involved in working memory in healthy subjects.

This study provides evidence that, during the encoding/maintenance period in a visuospatial working-memory task, healthy volunteers show increased BOLD activation in the right ventral prefrontal cortex (BA 44/45/47), the right and left lateral premotor areas (BA 6), the right inferior frontal gyrus, the left posterior parietal cortex (BA 19/40/7), the left intraparietal cortex, the left medial parietal cortex (precuneus), the right inferior parietal cortex, the right prestriate cortex, and the right and left superior parietal lobule/intraparietal sulcus. These findings are consistent with observations reported elsewhere. D'Esposito *et al.* (1998) identified the right ventral prefrontal cortex and the left and right premotor areas as areas of increased activation during spatial working-memory tasks. The left intraparietal cortex was identified by Rowe & Passingham (2001) as activated during maintenance and response selection in a visuospatial working-memory task. The right inferior parietal and prestriate cortices and the left medial

parietal cortex were regions found by Rowe & Passingham (2001) to be activated during the process of selection from memory. Manoach *et al.* (2000) reported activation in the right and left superior parietal lobule/intraparietal sulcus in normals during performance of a verbal working-memory task. In the superior temporal gyrus, normal controls showed a small positive activation difference between the memory and control condition (memory minus control BOLD values) during the retention period and a larger positive activation difference (memory minus control BOLD values) during the retrieval period ('G' in Table 1). It should be noted that in the applications of significance probability mapping in Table 1, specific tests of right minus left difference were not reported. In the instances where both right- and left-sided regions were reported, we subjected our data to exploratory five-way ANOVA with hemisphere as an additional repeated-measures factor. In most cases, significant interactions with hemisphere were not found and no region produced a significant condition × task interaction.

Compared to healthy volunteers, SPD patients performing a visuospatial working-memory task show decreased BOLD activation in the left ventral prefrontal cortex (BA 44/45/47), the left superior frontal gyrus (BA 10), the left intraparietal cortex, and the left posterior inferior gyrus (BA 44) and decreased activation at a trend level in the left lateral premotor cortex (BA 6), and the left precentral gyrus during the period that they are maintaining the spatial locations in memory. In addition they show a trend for greater activation in the right middle frontal gyrus (BA 46) and the right prestriate cortex. In agreement with Kindermann *et al.* (2004) for the left superior temporal gyrus SPD patients showed less activation difference (memory condition minus control condition) than normal volunteers during the retention period ('G', Table 1).

While the present study is, to our knowledge, the only published study examining regional activity in SPD patients as they carry out a visuospatial working-memory task, functional imaging studies of SPD patients engaged in other working-memory tasks provide some convergent observations. Buchsbaum *et al.* (1997) found decreased activation in the precentral gyrus in their SPECT study of SPD patients carrying out the WCST. In a separate PET study of SPD patients carrying out a serial verbal learning task Buchsbaum *et al.* (2002) found decreased metabolic activity in BA 44.

We considered the alternative hypothesis that reduced BOLD activation might signify more efficient rather than impaired processing. However, recent evidence from event-related fMRI studies suggests that increased activation is associated with better performance (Rypma *et al.* 2002, Rypma & D'Esposito, 2003). It is possible, however, that more efficient processing could be associated with a different regional allocation of resources in which activity in certain regions would be diminished but this would be compensated for by increased activity in other regions. This possibility is suggested by our finding that there were increases in BOLD signal in the right middle frontal gyrus (BA 46) and the right prestriate cortex.

Some but not all of the areas in which we found decreased activation have also been found to have activation differences between normals and patients with schizophrenia although BA 44 (inferior posterior frontal cortex) showed activation in patients with schizophrenia but not normal controls (Manoch *et al.* 2000). This suggests that normals and patients with SPD and schizophrenia may show different compensatory activation patterns.

There are a number of limitations to the present study. First, the small sample size limits the generalizability and power of the study and may explain our failure to find involvement of other regions in spatial working memory reported in the literature. Power estimates based on the fMRI area underneath the curve to estimate condition × diagnostic group interactions for the memory retention period showed medium to large effect sizes but limited power (e.g. condition difference scores for left dorsolateral prefrontal cortex (DLPFC) and lateral premotor area (LPM) had 34% power for a two-tailed $p < 0{\cdot}05$ difference between groups). However despite the small sample size we were able to replicate a sizable number of previously reported findings in normals. A second possible limitation is our transformation of all subjects' anatomic and BOLD images to a common Talairach space. While this method makes it possible to compare our findings directly with those of others, if there were systematic ana-

tomical differences between the SPD and HC groups, a given Talairach location in the normalized brain might correspond to different anatomical regions in the two groups, introducing artifactual findings. To test for this possibility, we undertook an analysis to determine the extent to which possible morphological differences between SPD and HC subjects could lead to systematic differences in the Talairach transformation. The Talairach transformation adjusts the brain proportionately according to six measured values, the anterior to posterior commissure (AC–PC) distance, the anterior to AC distance, the PC to posterior distance, the AC to left and right brain margins and the superior to inferior brain dimensions. We measured these parameters in a group of 22 HC subjects, 20 schizophrenia patients and six SPD patients and found no significant differences between the groups. This makes it unlikely that our finding of differential activation between groups is an artifact of the transformation to a common Talairach metric. Variation in the cortical folding and position within the cortical surface may not be fully adjusted by the Talairach transformation and would tend to diminish power to detect group differences and condition effects. Choosing the Talairach coordinates of the center of a maximum effect from an independent study and the use of the appropriate $p < 0{\cdot}05$ statistical level would tend to counter the power deficit problems associated with subject number, brain shape and cortical folding variation.

This study provides evidence that, compared to healthy volunteers, SPD patients show decreased activation during the maintenance period in a visuospatial working-memory task, in a number of regions associated with working memory. Since patients did not differ in task performance from normal subjects, this suggests that some alternative area processed information not processed in the prefrontal region. Two candidate regions are the right middle frontal gyrus (Talairach coordinates: 35, 31, 40) and the right prestriate cortex (Talairach coordinates: 16, −94, 2), where there was a trend level increase in activity in patients compared to normals. A larger sample will be necessary to confirm this, especially since the areas used in compensation for frontal deficits may be idiosyncratic. In addition, by demonstrating increased activation during the task in healthy volunteers in ROIs reported in the literature, this study provides partial replication of these studies.

ACKNOWLEDGMENTS

This work was supported in part by the Mental Illness Research Education and Clinical Center, VISN 3 Veterans Health Administration and a grant (5MO1 RR00071) for the Mount Sinai General Clinical Research Center from the National Center for Research Resources, National Institutes of Health.

DECLARATION OF INTEREST

None.

REFERENCES

Andreasen, N., O'Leary, D., Flaum, M., Nopoulos, P., Watkins, G., Boles-Ponto, L. & Hichwa, R. (1997). Hypofrontality in schizophrenia: distributed dysfunctional circuits in neuroleptic-naive patients. *Lancet* **349**, 1730–1734.

Bollini, A. M., Arnold, M. C. & Keefe, R. S. (2000). Test-retest reliability of the dot test of visuospatial working memory in patients with schizophrenia and controls. *Schizophrenia Research* **45**, 169–173.

Buchsbaum, M. S. & Hazlett, E. A. (1998). Positron emission tomography studies of abnormal glucose metabolism in schizophrenia. *Schizophrenia Bulletin* **24**, 343–364.

Buchsbaum, M. S., Nenadic, I., Hazlett, E. A., Spiegel-Cohen, J., Fleischman, M. B., Akhavan, A., Silverman, J. M. & Siever, L. J. (2002). Differential metabolic rates in prefrontal and temporal Brodmann areas in schizophrenia and schizotypal personality disorder. *Schizophrenia Research* **54**, 141–150.

Buchsbaum, M. S., Hazlett, E. A., Haznedar, M., Spiegel-Cohen, J. & Wei, T. C. (1999). Visualizing fronto striatal circuitry and neuroleptic effects in schizophrenia. *Acta Psychiatrica Scandinavica* **99** (Suppl. 395), 129–137.

Buchsbaum, M. S., Trestman, R. L., Hazlett, E., Siegel Jr., B. V., Schaefer, C. H., Luu-Hsia, C., Tang, C., Herrera, S., Solimando, A. C., Losonczy, M., Serby, M., Silverman, J. & Siever, L. J. (1997). Regional cerebral blood flow during the Wisconsin Card Sort Test in schizotypal personality disorder. *Schizophrenia Research* **27**, 21–28.

Callicott, J. H., Mattay, V. S., Verchinski, B. A., Marenco, S., Egan, M. F. & Weinberger, D. R. (2003). Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. *American Journal of Psychiatry* **160**, 2209–2215.

Callicott, J. H., Ramsey, N. F., Tallent, K., Bertolino, A., Knable, M. B., Coppola, R., Goldberg, T., van Gelderen, P., Mattay, V. S., Frank, J. A., Moonen, C. T. & Weinberger, D. R. (1998). Functional magnetic resonance imaging brain mapping in psychiatry: methodological issues illustrated in a study of working memory in schizophrenia. *Neuropsychopharmacology* **18**, 186–196.

D'Esposito, M., Aguirre, G. K., Zarahn, E., Ballard, D., Shin, R. K. & Lease, J. (1998). Functional MRI studies of spatial and nonspatial working memory. *Brain Research. Cognitive Brain Research* **7**, 1–13.

Fleming, K., Goldberg, T. E., Binks, S., Randolph, C., Gold, J. M. & Weinberger, D. R. (1997). Visuospatial working memory in patients with schizophrenia. *Biological Psychiatry* **41**, 43–49.

Fletcher, P. C., McKenna, P. J., Frith, C. D., Grasby, P. M., Friston, K. J. & Dolan, R. J. (1998). Brain activations in schizophrenia during a graded memory task studied with functional neuroimaging. *Archives of General Psychiatry* **55**, 1001–1008.

Hofer, A., Weiss, E. M., Golaszewski, S. M., Siedentopf, C. M., Brinkhoff, C., Kremser, C., Felber, S. & Fleischhacker, W. W. (2003*a*). An fMRI study of episodic encoding and recognition of words in patients with schizophrenia in remission. *American Journal of Psychiatry* **160**, 911–918.

Hofer, A., Weiss, E. M., Golaszewski, S. M., Siedentopf, C. M., Brinkhoff, C., Kremser, C., Felber, S. & Fleischhacker, W. W. (2003*b*). Neural correlates of episodic encoding and recognition of words in unmedicated patients during an acute episode of schizophrenia: a functional MRI study. *American Journal of Psychiatry* **160**, 1802–1808.

Jonides, J., Smith, E. E., Koeppe, R. A., Awh, E., Minoshima, S. & Mintun, M. A. (1993). Spatial working memory in humans as revealed by PET. *Nature* **363**, 623–625.

Keefe, R. S., Lees-Roitman, S. E. & Dupre, R. L. (1997). Performance of patients with schizophrenia on a pen and paper visuospatial working memory task with short delay. *Schizophrenia Research* **26**, 9–14.

Kindermann, S. S., Brown, G. G., Zorrilla, L. E., Olsen, R. K. & Jeste, D. V. (2004). Spatial working memory among middle-aged and older patients with schizophrenia and volunteers using fMRI. *Schizophrenia Research* **68**, 203–216.

Kumari, V., Gray, J. A., Geyer, M. A., ffytche, D., Soni, W., Mitterschiffthaler, M. T., Vythelingum, G. N., Simmons, A., Williams, S. C. & Sharma, T. (2003). Neural correlates of tactile prepulse inhibition: a functional MRI study in normal schizophrenic subjects. *Psychiatry Research* **122**, 99–113.

Manoach, D. S. (2003). Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings. *Schizophrenia Research* **60**, 285–298.

Manoach, D. S., Gollub, R. L., Benson, E. S., Searl, M. M., Goff, D. C., Halpern, E., Saper, C. B. & Rauch, S. L. (2000). Schizophrenic subjects show aberrant fMRI activation of dorsolateral prefrontal cortex and basal ganglia during working memory performance. *Biological Psychiatry* **48**, 99–109.

Manoach, D. S., Press, D. Z., Thangaraj, V., Searl, M. M., Goff, D. C., Halpern, E., Saper, C. B. & Warach, S. (1999). Schizophrenic subjects activate dorsolateral prefrontal cortex during a working memory task, as measured by fMRI. *Biological Psychiatry* **45**, 1128–1137.

McCarthy, G., Blamire, A. M., Puce, A., Nobre, A. C., Bloch, G., Hyder, F., Goldman-Rakic, P. & Shulman, R. G. (1994). Functional magnetic resonance imaging of human prefrontal cortex activation during a spatial working memory task. *Proceedings of the National Academy of Sciences USA* **91**, 8690–8694.

Park, S., Holzman, P. S. & Lenzenweger, M. F. (1995). Individual differences in spatial working memory in relation to schizotypy. *Journal of Abnormal Psychology* **104**, 355–363.

Park, S. & McTigue, K. (1997). Working memory and the syndromes of schizotypal personality. *Schizophrenia Research* **26**, 213–220.

Park, S., Puschel, J., Sauter, B. H., Rentsch, M. & Hell, D. (1999). Spatial working memory deficits and clinical symptoms in schizophrenia: a 4-month follow-up study. *Biological Psychiatry* **46**, 392–400.

Roitman, S. E., Mitropoulou, V., Keefe, R. S., Silverman, J. M., Serby, M., Harvey, P. D., Reynolds, D. A., Mohs, R. C. & Siever, L. J. (2000). Visuospatial working memory in schizotypal personality disorder patients. *Schizophrenia Research* **41**, 447–455.

Rowe, J. B. & Passingham, R. E. (2001). Working memory for location and time: activity in prefrontal area 46 relates to selection rather than maintenance in memory. *Neuroimage* **14**, 77–86.

Rypma, B., Berger, J. S. & D'Esposito, M. (2002). The influence of working-memory demand and subject performance on prefrontal cortical activity. *Journal of Cognitive Neuroscience* **14**, 721–731.

Rypma, B. & D'Esposito, M. (2003). A subsequent-memory effect in dorsolateral prefrontal cortex. *Brain Research. Cognitive Brain Research* **16**, 162–166.

Siever, L. J., Koenigsberg, H. W., Harvey, P., Mitropoulou, V., Laruelle, M., Abi-Dargham, A., Goodman, M. & Buchsbaum, M. (2002). Cognitive and brain function in schizotypal personality disorder. *Schizophrenia Research* **54**, 157–167.

Weinberger, D. R. & Berman, K. F. (1996). Prefrontal function in schizophrenia: confounds and controversies. *Philosophical Transactons of the Royal Society of London B: Biological Sciences* **351**, 1495–1503.

Weinberger, D. R., Berman, K. F. & Illowsky, B. P. (1988). Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. III. A new cohort and evidence for a monoaminergic mechanism. *Archives of General Psychiatry* **45**, 609–615.