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An fMRI study of prefrontal dysfunction and symptomatic recovery in schizophrenia

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Smee C, Krabbendam L, O'Daly O, Prins A-M, Nalesnik N, Morley L, Samson G, Shergill S. An fMRI study of prefrontal dysfunction and symptomatic recovery in schizophrenia.

Objective: Prefrontal cortical dysfunction has been implicated in the pathophysiology of schizophrenia but it is unclear to what extent these are related to changes in symptomatology as well as task demand.
Method: We examined the neural correlates of symptom change and task demand during a longitudinal functional magnetic resonance imaging (fMRI) study using a verbal fluency task with differential task demands in patients with schizophrenia and matched healthy control subjects. The fMRI data were acquired using clustered acquisition technique, enabling ongoing monitoring of behavioural responses, in the patient group on two occasions separated by 6–8 weeks, and the control group at baseline.
Results: Positive psychotic symptoms were significantly reduced over the 6–8-week duration of the study. This change was associated with increased activation within the left middle frontal gyrus and decreased activation of the left precuneus. An interaction between symptom change and task demand was evident in the activation of the left middle frontal gyrus. The decrease in positive symptoms was associated with normalisation of activation in the dorsolateral prefrontal cortex and a decrease in parietal activation during the verbal fluency task.
Conclusion: The data supports the role of dysfunctional prefronto-parietal relationships in the genesis of positive psychotic symptoms.

Key words: positive symptoms; verbal fluency; prefrontal cortex; schizophrenia; neuroimaging

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Significant Outcomes

- Increases in the activation of the left middle frontal gyrus, as positive psychotic symptoms decrease, commensurate with normalisation of prefrontal activity.
- A decrease in parietal (left precuneus) activation with time, although this did not show a correlation with change in positive symptoms, it is in accordance with the return of prefrontal inhibitory control over these more posterior cortical regions.
- The main effect of group showed attenuation in a network of areas including the cerebellum, thalamus, cingulate gyrus and a large prefrontal cluster including inferior and middle frontal gyri in the patient group compared to the control group. Further analysis confirmed an interaction between group and task demand in the left cingulate gyrus and cerebellum.

Limitations

- There is the issue of generalisability of these results from the analysis of a relatively small number of subjects.
- The non-parametric statistical approach used in the analysis of the imaging data is robust, and we have used stringent thresholds for all of our analyses to minimise any Type I errors; the significance threshold was set to give less than one false positive cluster over the whole brain.
- The sensory modality in which the cue for word generation is presented will also influence the results – we have used auditory stimuli which may have an effect of reducing our ability to detect temporal cortex activation although similar results have been obtained where investigators have used visual stimuli.

Introduction

Following the initial finding of decreased frontal metabolism by Ingvar and Franzen (1), there has been continuing interest in the blood flow changes in frontal brain regions in patients with schizophrenia. Neuroimaging of the frontal cortex has demonstrated its involvement in a broad range of different cognitive domains (2), many of which have been shown to be dysfunctional in patients with schizophrenia; these include aspects of response selection, executive comparison, working memory, episodic memory, problem solving and perception (3). However, variations in the performance of cognitive tasks have led to concern that neuroimaging comparisons between patient and control groups may be confounded by poorer task performance in the patient group (4–6). This has been addressed by the adoption of experimental designs using parametrically varied task demands, which permit more careful attention to matching equivalent performance between different groups of subjects. This approach, applied mainly to working and episodic memory paradigms, has suggested that patients with schizophrenia may have normal or even increased frontal activation, compared with healthy controls, when task demand is relatively low; but significantly attenuated activation as the task demand is increased (4, 7, 8).

Research comparing symptomatic and remitted patients suggests that there may be differences in activation which are related to symptomatology (9–12). The use of a longitudinal design permits evaluation of both task demand and symptomology. Functional magnetic resonance imaging (fMRI) has been shown to be both reliable and replicable in both healthy controls (2) and stable patients (13), which facilitates longitudinal studies. Spence et al. (14) have used positron emission tomography (PET) to show that patients with high symptom scores showed hypofrontality in the left dorsolateral prefrontal cortex (DLPFC), but that activity within this region returned to normal when symptoms had decreased following a second scan.

Verbal fluency is used as a standard neuropsychological test of language production requiring subjects to generate words in response to cues (10, 15–17). The functional anatomy of verbal fluency has been characterised in normal subjects (18, 19); the cortical regions consistently associated with this task include the left middle and inferior frontal gyri (17, 19–22, 26–28), the cingulate gyrus (17, 22, 25, 28–31), as well as the right cerebellum and the temporoparietal cortex (17, 27, 29, 31, 32). Increased task demand had been associated with increased prefrontal and anterior cingulate gyrus activation in healthy controls (17), while patients with schizophrenia fail to demonstrate this 'normal' response to the increased task demand (12, 17, 33). Of the regions showing a task-related increase in activation, only the anterior cingulate gyrus showed an interaction between task demand and symptomatic status (12).

In this study, we used fMRI to examine the effects of task demand and symptom change in patients with a diagnosis of schizophrenia, using a letter verbal fluency paradigm with online performance monitoring (12, 17, 20, 34, 35), within a factorial design.

Aims of the study

We hypothesised that i) at baseline, the main effect of increased task difficulty would be reflected in increased activation of the anterior cingulate gyrus and the left prefrontal cortex, while the main effect of group would demonstrate decreased activation within these regions in the patient group; we anticipated that the anterior cingulate gyrus would demonstrate a significant interaction effect between task difficulty and subject group; ii) at follow-up, the main effect of time would be evident in increased activation of the left prefrontal cortex and that this would correlate with the change in the positive symptoms.

Material and methods

Subjects

Twelve patients with a DSM-IV diagnosis of schizophrenia (American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders) (36) were recruited from wards and clinics at the Maudsley Hospital, London. One patient was excluded from analysis because of failure to correctly perform the task during the imaging and two failed to attend for their second scan. The age of the remaining nine patients, of whom eight were men and one was woman, was 36.8 ± 8.6 years (mean ± standard deviation); range 25–53. They had spent 13.2 ± 2.1 years in full-time education (range 10–16). The patients had been ill for 13.5 ± 9.5 years (range 5–33) and were receiving stable doses of antipsychotic medication with a chlorpromazine equivalent of 523 ± 455 mg/day (range 166–1666; seven treated with conventional and two with atypical antipsychotics). Symptoms were assessed using the Positive and Negative Symptoms Scale (PANSS) immediately prior to scanning on both occasions (37). Their total score was 55.7 ± 16.1

Table 1. Demographics and clinical features of patients and controls

	Patients		Controls	
	Mean (SD)	Range	Mean (SD)	Range
Gender (m : f)	8 : 1		5 : 4	
Age (years)	36.8 (8.6)	25–53	32.6 (6.5)	25–45
Years in full-time education	13.2 (2.1)	10–16	15.7 (3.1)	10–19
Antipsychotic CPZ equivalent (mg/day)	523 (455)	166–1666		
PANNS total score baseline	55.7 (16.1)	31–85		
PANNS total score follow-up	11.4 (4.0)	7–18		

(range 31–85) at baseline and 48.3 ± 6.6 (range 35–57) at follow-up, with mean positive PANSS scores of 15.3 ± 7.5 (range 7–28) at baseline and 11.4 ± 4.0 (range 7–18) at follow-up (Table 1).

Nine healthy comparison controls (five men) were scanned; these controls were matched to the patients for age (32.6 ± 6.5 years; range 25–45) and education (15.7 ± 3.1 years; range 10–19). There were no significant differences between patients and controls in age ($t_{1,16} = -1.17$; $P = 0.259$) or years spent in full-time education ($t_{1,16} = 2.00$; $P = 0.063$) (Table 1).

All subjects provided informed consent, and ethical approval was provided by the Institute of Psychiatry and Maudsley NHS Trust. All subjects were right-handed, as assessed with the Annett Handedness Inventory (38), and all were fluent native English speakers. Subjects were excluded from participation if they had a history of drug or alcohol abuse, neurological illness, head injury, speech or hearing difficulties, or any contraindications to MRI scanning such as metal implants.

Experimental design

The first phase of the study investigated the effect of two factors during the verbal fluency task: subject group (patients vs. controls) and task demand (easy vs. difficult letters; manipulated within controls). It therefore took the form of a 2 × 2 mixed design. The second longitudinal phase of this study compared patients scanned at two time points, baseline and follow-up, separated by 6–8 weeks, using a within controls design examining the two factors, symptom change and task demand.

The verbal fluency paradigm was specifically designed for patient groups (39) using a paced design to minimise between-group performance differences. In brief, each task consisted of a periodic block design with alternating periods of baseline and experimental condition (60 s each), which were repeated five times across a 10-min scanning schedule. During the task, the participant was presented with a stimulus cue every 6 s and responded overtly with a single word in a 4-s quiet period. This was followed by 2 s of compressed sequence acquisition (34). The experimental condition consisted of letter-based word generation, in which the participant heard an auditory cue consisting of a letter and responded overtly with a word beginning with that letter, keeping their eyes closed throughout the task to prevent visual interference. On failure to generate an appropriate word, the participant was required to say the word 'pass' during the quiet, 4-s response time. At the start of each block, to ensure that the participant heard the cue correctly, the first presentation consisted of the letter followed by the corresponding word from the phonetic alphabet (e.g. 'a for alpha'), during which they remained silent. There then followed nine successive presentations of the same letter cue, after each of which the participant responded with a word beginning with that letter. Subjects were instructed to avoid responding with repetitions, grammatical variations and plurals of previously generated words, and using proper nouns. Each of the verbal fluency blocks consisted of ten repetitions of a different letter (F, A, S, R, P). Of these, F and A were classified as relatively 'Difficult' letters and S, R and P were classified as relatively 'Easy' letters, on the basis of error rates in a previous verbal fluency study in healthy controls from the same geographical area (17). The order of experimental blocks was counterbalanced across the participants. During the baseline condition, the participant was cued by auditory presentation of the word 'rest' which they were required to repeat in the 4-s period.

Functional MRI data acquisition

Data were acquired using a 1.5 T GE Signa Neuro-optimized MR System (GE, Milwaukee, WI, USA) at the Maudsley Hospital, London. A quadrature birdcage head coil was used for RF transmission and reception. One hundred T2*-weighted gradient echo-planar images depicting blood oxygenation level-dependent contrast were acquired from 16 non-contiguous planes parallel to the anterior commissure-posterior commissure plane [slice thickness 7 mm, slice gap 0.7 m, repetition time (TR) 6000 ms, echo time (TE) 40 ms, flip angle = 90°]. A compressed pulse sequence was used where the data acquisition took place within the last 2 s of each TR, with 4 s during which the participant provided an overt response when there was no sound of the MR

gradients. A high-resolution inversion recovery echo-planar image of the whole brain was also obtained [TE = 73 ms, inversion time (TI) = 180 ms, TR = 16 000 ms] for subsequent registration to the standard stereotaxic space of Talairach and Tournoux (40).

Image analysis

Movement estimation and correction procedures as described by Friston et al. (41) were first applied to the data. The data were then analysed by convolving the experimental design with two Poisson functions parameterising the haemodynamic delays of 4 and 8 s (41). The weighted sum of the two convolutions giving the best (least squares) fit to the time series at each voxel was computed, and the sums of squares attributed to the fitted model and the residuals were evaluated. The ratio of model/residual sum of squares (SSQ ratio) computed at each voxel was then evaluated for significance by comparison with the null distribution of the same statistic computed by repeating the fitting procedure 10 times at each voxel after wavelet-based random permutation of the time series and combining data across all voxels. This non-parametric procedure has been reliably validated for use with fMRI time series analyses and shown to give excellent Type I error control (42). Statistical testing at group level was carried out after transformation of the SSQratio maps obtained from the observed and randomised data into standard space (29). Median activation maps were computed across subjects and thresholded at a voxel-wise probability of a false activation of $P < 0.025$ using the spatially transformed randomised data maps to construct the distribution of median SSQ ratios under the null hypothesis of no significant response. Both within-group and between-group comparisons were then carried out using cluster-level statistics (43) and random permutation of group membership to obtain the distribution of SSQratio differences between groups under the null hypothesis of no group difference in level of response. A conservative significance level was adopted for all between-group comparisons in which *P*-values were set to ensure less than one false positive cluster per image. At baseline, we examined the main effects of task demand and the main effect of subject group and any regions of significant interaction. At follow-up, we examined the main effects of time and difficulty and extracted the mean SSQ from the regional clusters regions showing a difference over time and examined these for correlations with change in the PANNS positive subscale.

Results

Behavioural results – baseline

Behavioural data were unavailable for one control subject. Therefore, the remaining eight controls and nine patients were included in the analysis of behavioural responses for baseline.

A 2×2 ANOVA comparing error rates between groups (patients vs. controls) and difficulty levels (easy vs. hard) at baseline revealed a highly significant main effect of difficulty level ($F_{1,32} = 7.6$; $P < 0.01$), with hard letters yielding 2.2 ± 1.9 (mean ± standard deviation) erroneous responses in a total of 20 trials, and easy letters yielding 1.3 ± 1.8 erroneous responses in 30 trials. This validates the selection of the stimuli, confirming that it is more difficult to generate words from letters that were classified as relatively 'difficult' (F and A) against those classified as relatively 'easy' (S, R and P) (17), and that the experimental conditions successfully manipulated task demand.

There was no significant main effect of group at baseline ($F_{1,15} = 0.20$; $P > 0.70$), the overall number of erroneous responses out of 50 trials for controls and patients being 1.1 ± 1.3 (range 0–5 errors) and 2.2 ± 2.2 (range 0–9) respectively. Therefore, any main effects revealing differential neural responses between patients and controls are unlikely to be because of the systematic between-group differences in performance. The mean number of errors for controls was 0.7 ± 0.9 words in 30 trials (range 0–3 errors) in the easy condition and 1.7 ± 1.5 words in 20 trials (range 0–5 errors) in the difficult condition ($t_{1,15} = 2.7$; $P < 0.008$). The mean number of errors for patients was 1.9 ± 2.5 words in 30 trials (range 0–9 errors) in the easy condition and 2.7 ± 2.1 words in 20 trials (range 0–7 errors) in the difficult condition ($t_{1,17} = 1.5$; $P > 0.08$). There was no significant interaction between group and difficulty level ($F_{1,17} = 0.20$; $P > 0.05$). Almost all the errors were repetitions or use of plurals.

Follow-up

A main effect of difficulty ($F_{1,17} = 4.5$; $P < 0.05$) was also evident during a comparison of error rates in patients at follow-up to their performance at baseline in the easy and hard letter conditions, with hard letter fluency yielding 3.0 ± 2.4 (mean ± standard deviation) erroneous responses in a total of 20 trials and easy letter fluency yielding 1.9 ± 2.1 erroneous responses in a total of 30 trials.

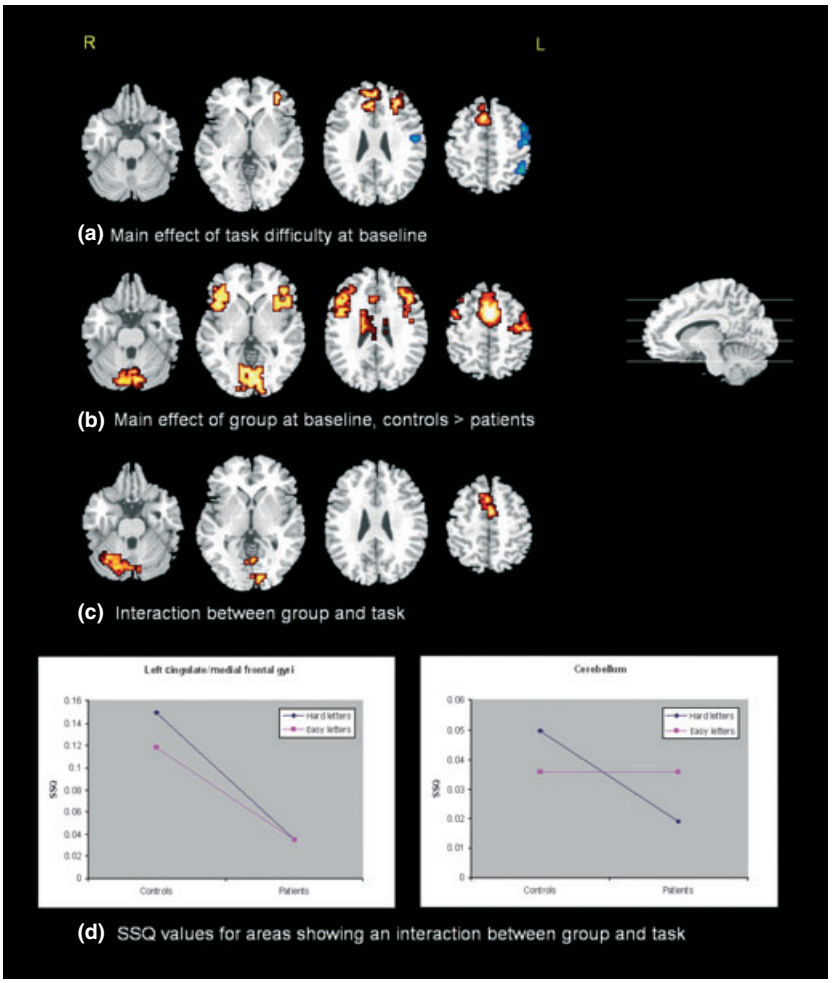

Fig. 1. (a) An increase in task difficulty, regardless of group, is accompanied by an increase in neural response of the left middle frontal and anterior cingulate gyri, while the left precentral gyrus is more active during the easy condition. Clusters in yellow/orange demonstrate areas more active during the difficult condition while the cluster in blue show greater activation during the easy condition. (b) Main effect of group at baseline illustrates an attenuation of activation in the bilateral lingual gyrus, bilateral inferior frontal gyrus, bilateral medial frontal/cingulate gyri and thalamus in patients, irrespective of task demand. (c) An interaction between task demand and group at baseline is seen in the left medial frontal/cingulate gyri, cerebellum and left lingual gyrus. (d) Graphs illustrating SSQ values for areas showing the interaction. Left hemisphere appears to the right of the page. Lines on sagittal slices correspond to the orientation of the axial slices.

A paired *t*-test comparing PANSS scores at baseline and follow-up shows a significant decrease in positive symptoms by follow-up ($t_{1,8} = 2.3$; $P < 0.02$), but no significant decrease in any of the negative or general subscales or in the Total PANSS score ($t_{1,8} = 1.7$, $P > 0.07$).

fMRI results – baseline

Main effect of task difficulty. Individual analysis of the two difficulty levels at baseline revealed more activation in the left precentral gyrus during the easy condition with the difficult task condition resulting in increased neural response in the left middle frontal gyrus and anterior cingulate (Fig. 1a and Table 2a).

Main effect of group. The patient group showed significantly attenuated power of response within the bilateral inferior frontal extending into the middle frontal gyri, the bilateral anterior cingulate/medial frontal gyri, the thalamus and bilateral cerebellum extending into the lingual gyrus (Fig. 1b and Table 2b). There were no regions that were significantly more active in the patient group than the control group.

Interaction of task difficulty × group. An interaction between group and task demand at baseline was evident in the anterior cingulate gyrus, the cerebellum and the left lingual gyrus (Fig. 1c and Table 2c). Graphs plotting the SSQ values for the interaction illustrate an attenuated response within the left cingulate/medial frontal gyri in the patients – with no apparent difference in response to increased task demand, while controls show greater activation in this region and a further increase in line with task demand (Fig. 1d). Neural response in the cerebellum was similar during the easy phase of the task but while controls demonstrated an increased response with increased task demand, the patients showed an attenuated cerebellar response (Fig. 1d).

Follow-up

Main effect of time (change in positive symptoms). There was a main effect of time evident in

Table 2. Main regional foci of brain activation by the verbal fluency task at baseline in healthy controls and patients which demonstrates: (a) main effect of group, (b) main effect of task difficulty, and (c) interaction between group and difficulty

Cerebral region (Brodmann area)	Number of voxels	Probability	Talairach coordinates		
			x	*y*	*z*
(a) Main effect of group: baseline					
Controls > Patients					
Bilateral lingual gyrus/cerebellum (18)	326	0.0003	0	−81	−2
R Inferior frontal gyrus (44)	277	0.0003	43	33	4
L Inferior frontal gyrus (44)	244	0.0011	−40	33	9
Bilateral medial frontal/cingulate gyrus (67)	238	0.0003	0	15	42
Thalamus (69)	163	0.0055	−4	−15	9
(b) Main effect of task difficulty: baseline					
Easy letters					
L Precentral gyrus (4)	108	0.0068	−51	−7	31
Hard letters					
Anterior cingulate (9)	141	0.0040	−4	48	9
L Middle frontal gyrus (45)	54	0.0085	−29	41	15
(c) Interaction					
Controls > Patients					
Cerebellum	94	0.0080	−4	−67	−40
L Medial frontal/cingulate gyri (6)	81	0.0009	−4	4	48
L Lingual gyrus (18)	65	0.0096	−4	−74	−2

The *x*, *y* and *z* coordinates refer to position within the stereotactic space according to the Talairach and Tournoux atlas (40).
R, right hemisphere; L, left hemisphere.

the left middle frontal gyrus and the medial frontal gyrus and left precuneus (Fig. 2a and Table 3a). A decrease in positive symptoms over time was associated with increased activation of the middle frontal gyrus and decrements in precuneus and medial frontal activation.

Only the change in activation within the left middle frontal gyrus SSQ demonstrated a significant inverse correlation with the change PANNS positive score (Pearson correlation −0.73; $P < 0.05$).

Main effect of task difficulty. A main effect of task difficulty was evident in a cluster extending from the left inferior frontal to the middle frontal gyrus and in the cerebellum. Both showed a significant decrease in activation as task difficulty was increased (Fig. 2b and Table 3b).

Interaction of task difficulty × time (symptom change). A significant interaction between time (symptom change) and task demand was evident in the left middle frontal gyrus and left precuneus, as seen in Fig. 2c and Table 3c. There was an increase in activation within the middle frontal gyrus as positive symptoms decreased over time; however, this increase in activation was greater for the easier condition compared to the more difficult condition. The precuneus showed an inverse change to that in the prefrontal cortex, with decreased activation over time but a relatively greater decrease in the easy condition than the more difficult condition (Fig. 2d).

Discussion

This is the first fMRI study to examine the changes in functional neuroanatomy associated with symptom change in the same patients with schizophrenia using an overt, paced verbal fluency task with varied task demand. There was an increase in the activation of the left middle frontal gyrus, as positive psychotic symptoms decreased, commensurate with normalisation of prefrontal activity. Interestingly, these changes were more marked for the easy condition than the more difficult condition, suggesting that there is a non-linear relationship in patients with schizophrenia and that there may be evidence of a form of 'inverted U' shaped response in the prefrontal cortex (7, 44, 45). We also found a decrease in parietal (left precuneus) activation with time, although this did not show a correlation with change in positive symptoms, it is in accordance with the return of prefrontal inhibitory control over these more posterior cortical regions (14, 34).

We found that the main effect of task difficulty activated the anticipated left prefrontal regions as well as the anterior cingulate gyrus and cerebellum, consistent with most previous verbal fluency studies. The main effect of group showed attenuation in a network of areas including the cerebellum, thalamus, cingulate gyrus and a large prefrontal cluster including inferior and middle frontal gyri in the patient group. Further analysis confirmed an interaction between group and task demand in the left cingulate gyrus and cerebellum. As expected, healthy controls showed increased activation in the anterior cingulate in line with task demand (12), while patients failed to show increased activation with increased task demand. Interestingly, controls showed a similar increase in cerebellar activation during the more difficult condition while patients showed an inverse, decreased, response as task demand increased. Previous verbal fluency studies in patients with schizophrenia have demonstrated attenuated activation, in the left inferior and middle frontal gyri and right inferior frontal gyrus (22, 32) and anterior cingulate cortex (22, 46). However, some other studies have shown no difference in frontal activation between patients compared with comparison controls (19, 24, 31, 47). The discrepancies between different studies may have reflected their varying ability to monitor behavioural results online.

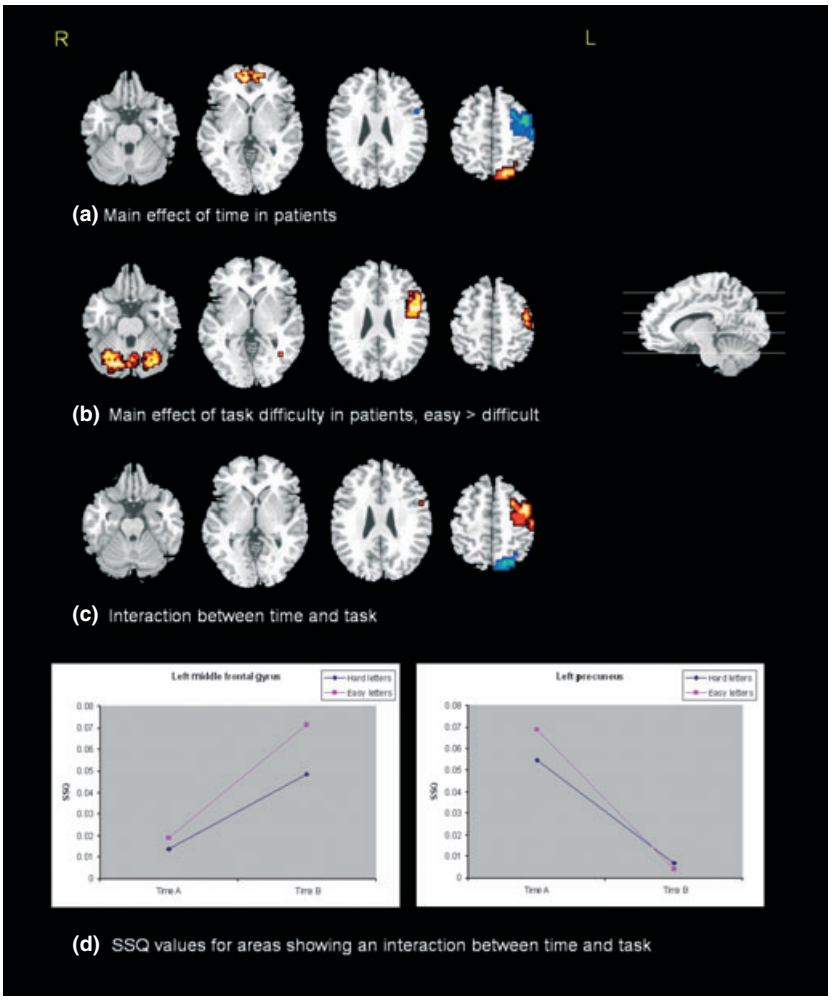

Fig. 2. (a) Changes in cortical activation from baseline to follow-up in patients with schizophrenia during verbal fluency task, irrespective of task demand. Greater activation was seen at baseline in the medial frontal gyrus and the precuneus, while the middle frontal gyrus was more active in patients at follow-up. Clusters in yellow/orange demonstrate greater activation at baseline while clusters in blue/green show greater activation at follow-up. (b) Patients show attenuation in the precuneus and inferior frontal gyrus during hard letter fluency compared to easy letter fluency, irrespective of time. (c) Activation maps of mean SSQ ratios showing effect of interaction between increased task demand and changes in activation from baseline to follow-up in the middle frontal gyrus and precuneus. Clusters in yellow/orange show greater difference between conditions at follow-up while clusters in blue demonstrate a smaller difference between conditions at follow-up. (d) Graphs illustrating SSQ values for areas showing the interaction. Left hemisphere appears to the right of the page. Lines on sagittal slices correspond to the orientation of the axial slices.

Table 3. Main regional foci of brain activation by the verbal fluency task in schizophrenic subjects which illustrates (a) main effect of time, (b) main effect of task difficulty, and (c) interaction between time and task difficulty

Cerebral region (Brodmann area)	Number of voxels	Probability	Talairach coordinates		
			x	*y*	*z*
(a) Main effect of time					
Baseline > Follow-up					
L Precuneus (7)	72	0.0012	−14	−70	42
Bilateral medial frontal gyrus (11)	66	0.0094	4	56	−13
Follow-up > Baseline					
L Middle frontal gyrus (6)	154	0.0011	−40	0	48
(b) Main effect of task difficulty					
Easy > Hard					
Bilateral cerebellum	270	0.0005	25	−63	−40
L Inferior frontal gyrus (43)	134	0.0022	−51	7	20
(c) Interaction					
Area where the difference between easy and difficult is reduced at follow-up					
L Precuneus (7)	72	0.0012	−14	−70	42
Area where the difference between easy and difficult is increased at follow-up					
L Middle frontal gyrus (6)	154	0.0011	−40	0	48

The *x*, *y* and *z* coordinates refer to position within the stereotactic space according to the Talairach & Tournoux atlas.
R, right hemisphere; L, left hemisphere.

Some fMRI investigations into verbal fluency have used an overt design in which responses are articulated, rather than a covert (silent) design, enabling measurement of task performance (48–51). However, conventional acquisition sequences generate a continuous background scanner noise, making it difficult to hear subject responses and introducing potentially confounding effects on activation (34, 52). Concerns have additionally been raised about the modulatory effects of background noise on auditory feedback and articulatory control (17, 53, 54) and about increased movement artefacts as a result of overt speech production (17, 20, 28, 32, 34, 52, 55). This study was able to overcome some of these problems using a modified partially silent acquisition to allow online monitoring of responses (34).

Recent studies have moved beyond 'hypofrontality' (14, 32, 56) and suggested paying attention to the modulatory role of task performance (7, 48, 57, 58). Working memory experiments have suggested the DLPFC activation increases as task

demand increases until capacity is exceeded, resulting a decrease in prefrontal activity, often characterised as an 'inverted U' neural response profile? (44). Furthermore, it has been suggested that cortical inefficiency could result in reduced task-related capacity expressed as a shift to the left of the 'inverted U' response proposed (44, 45). Thus, patients may show greater prefrontal activation during easy load conditions than when the task becomes more demanding. Similar data have been demonstrated for the anterior cingulated gyrus, where healthy controls show increased response in the anterior cingulate gyrus, while patients with schizophrenia fail to respond sufficiently to the increased task demand (12, 17, 33). In our study, at baseline the patients demonstrated an attenuation of the anterior cingulate gyrus in addition to a lack of demand-related activation. There were inverse activation in the cerebellum, and putatively these could be part of a compensatory mechanism in keeping with well-recognised cortico-thalamic feedback loops (33, 59).

The initial main effect of time suggests prefrontal recovery with decreases in positive symptoms, consistent with previous findings. The left precuneus showed less activation at follow-up, while there was an increase in the left middle frontal gyrus activation. This is in accord with the suggestion of a suppressive influence of the DLPFC on the precuneus in healthy controls (34). The interaction between task demand and time suggests that the hypofrontality in the left middle frontal gyrus may result in a failure to suppress activity within the left precuneus, with normalisation associated with decreased positive symptoms. Improvement in the easy condition is indicative of enhanced cortical efficiency as symptoms decrease. However, less improvement in the difficult condition suggests that normalisation is limited and prefrontal capacity remains constrained. A consistently higher level of neural response in the easy condition suggests that while patients with symptomatic recovery show a recovery of function in these areas, it is not to the same level as the healthy controls.

The precuneus has been associated with processes that may be involved in the verbal fluency task, such as attention shifting, decision-making, reasoning and a load-dependent relationship in memory retrieval (60–65). Additionally, it has been demonstrated that patients with schizophrenia show a stronger BOLD response in the precuneus when compared with controls during a verbal fluency task, suggesting that they fail to deactivate the precuneus (19); activation has also been related to the presence of passivity phenomena. We did not specifically assess the presence of, or changes in, passivity phenomena in this study, but it is possible that they could contribute to the changes seen in the PANSS positive subscale.

There are several potential limitations to this study. There is the issue of generalisability of these results from the analysis of a relatively small number of controls. The non-parametric statistical approach used in the analysis of the imaging data is robust, and we have used stringent thresholds for all of our analyses to minimise any Type I errors; the significance threshold was set to give less than one false positive cluster over the whole brain (23). The sensory modality in which the cue for word generation is presented will also influence the results – we have used auditory stimuli which may have an effect of reducing our ability to detect temporal cortex activation although similar results have been obtained where investigators have used visual stimuli (17). We employed a verbal repetition task as a baseline condition to enable comparisons between word generation with and without the need for lexical searching, although some investigators have used alternative comparison conditions such as paced counting (27) or a null/simple relaxation baseline (28, 30, 31, 66, 67).

Because there were no significant differences in behavioural performance between the groups, it appears to exclude a systemic effect on the behavioural change. The longitudinal patient design was in the same patient group with no additional variations related to gender differences. The results suggest that there is less activation in patients within the cingulate gyrus and cerebellum. However, it was not possible to tease out differential gender effects with in this small sample size. The literature suggests gender differences in cortical thickness in favour of the female right inferior parietal and posterior temporal regions (75), and these areas do not show a correlation with change in positive symptoms in our study.

Subject characteristics including symptomology and medication in the patient groups may also influence the between-group variability. Examining for medication effects within the patient group, we found no significant correlation of the activation maps with dosage equivalents of medication. The patients did not have any alterations in their antipsychotic medication during the two imaging sessions, thus changes are unlikely to be related to medication induced changes. This is in accord with the report of Spence et al. (19) who also failed to show any association between cerebral blood flow and medication in their PET study of verbal fluency. A recent metaanalysis of 155 brain imaging studies of schizophrenia found no support for

medication contributing significantly to differences between patients and controls (68), and similar findings of attenuated frontal blood flow have also been demonstrated in unmedicated patients (69). However, the long-term effects of antipsychotic medication on the morphology of the brain need to be taken into account. The literature suggests that neuroleptic exposure with typical antipsychotics increases the left anterior cingulate gyrus in volume, without displaying an increase in surface area, influenced by dose and time. There was, however, no correlation between PANNS outcome and morphology found (70). Recent systemic reviews by Smieskova et al. (71) and Navari et al. (72) suggest that antipsychotic treatment potentially contributes to brain structure changes. An enlargement of the thalamus as a result of treatment with atypical antipsychotics was observed (73, 76).

A passive auditory and visual stimulation experiment was run on all controls and again there were no significant changes between the two scans, therefore excluding any non-specific repetition or session effects. However, only the middle frontal changes correlated with positive symptom change and one cannot exclude practice effects from contributing to changes in activation within the medial frontal and parietal changes; certainly, future work could usefully include a specific control group to be imaged at both time points to exclude any subtle repetition effects on the task.

Another interpretation of the data could lie in abnormal lateralisation of the brain in schizophrenia (74). Where separation of the left lateralised phonological engram from the right lateralised semantic and pragmatic aspects also accentuates the propensity to psychosis (26).

We were interested in the relationship between frontal cortical activation and change in positive symptoms, while medication was kept stable. Over this time frame, we anticipated that negative and general symptoms were unlikely to change significantly, but that positive symptoms would be the most likely to show some fluctuation. While it was initially surprising to see that the patients showed a significant drop in their positive symptoms over this time, it is less surprising when one considers that they were being reviewed by the researchers on a weekly basis in the time between scans.

In summary, we have demonstrated that a decrease in positive symptoms in patients with schizophrenia is associated with partial recovery of hypofrontality in the DLPFC as well as a decrease in the activation in the precuneus, which supports the hypothesis that the prefrontal cortex normally inhibits effect over caudal regions and the failure of this inhibition may contribute to the generation of positive symptoms.

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Declaration of interest

None of the authors report any biomedical financial interests or potential conflicts of interest from January 2009.

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