Pathophysiology of 'positive' thought disorder in schizophrenia

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Background Formal thought disorder is a characteristic feature of psychosis, but little is known of its pathophysiology. We have investigated this in schizophrenia using positron emission tomography (PET).

Method Regional cerebral blood flow was measured using $H_2{}^{15}O$ and PET while six people with schizophrenia were describing a series of 12 ambiguous pictures which elicited different degrees of thought-disordered speech. In a within-subject design, the severity of 'positive' thought disorder was correlated with cerebral blood flow across the 12 scans in each subject.

Results Verbal disorganisation ('positive' thought disorder) was inversely correlated with activity in the inferior frontal, cingulate and left superior temporal cortex, and positively correlated with activity in the parahippocampal/anterior fusiform region bilaterally, and in the body of the right caudate ($P<0.001$). The total amount of speech produced (independent of thought disorder) was positively correlated with activity in the left inferior frontal and left superior temporal cortex.

Conclusions The severity of positive thought disorder was inversely correlated with activity in areas implicated in the regulation and monitoring of speech production. Reduced activity in these regions may contribute to the articulation of the linguistic anomalies that characterise positive thought disorder. The positive correlations between positive thought disorder and parahippocampal/anterior fusiform activity may reflect this region's role in the processing of linguistic anomalies.

Thought disorder is one of the most striking features of schizophrenia but one of the least understood. Factor analyses suggest that thought disorder is heterogeneous, with the bulk of the variance attributable to 'verbal disorganisation', a cluster of 'positive' features, such as neologisms, illogicality and distractibility (Andreasen & Grove, 1986; Liddle, 1987). In the present study we elicited varying degrees of verbal disorganisation by asking patients with schizophrenia to describe a series of ambiguous pictures. We then examined the relationship between the severity of verbal disorganisation and the distribution of regional cerebral blood flow (rCBF), measured using positron emission tomography (PET), in a within-subject design. On the basis of existing neuropsychological and neuroimaging data (Liddle & Morris, 1991; Liddle *et al*, 1992; Shenton *et al*, 1992; Nathaniel-James & Frith, 1996), we predicted that 'positive' thought disorder would be associated with functional changes in the inferior frontal, anterior cingulate and left superior temporal cortex.

METHOD

Subjects

Six right-handed men with DSM–IV (American Psychiatric Association, 1994) schizophrenia were recruited from the Maudsley and Charing Cross Hospitals, London. Subjects were selected if they were currently producing positive thought-disordered speech, did not show marked evidence of other psychotic phenomena and had a history of prominent thought disorder throughout their illness. Only subjects able to complete three trials of the task to be used during scanning, and who articulated positive thought-disordered speech on these trials, were included. All subjects were in a stable clinical condition and had been receiving regular doses of 'typical' antipsychotic medication for at least one month (mean dose 450 mg chlorpromazine equivalents, range 250–750). Their mean age and duration of illness were 34 (26–45) and 12 (3–19) years, respectively, while their mean premorbid verbal IQ (estimated with the National Adult Reading Test; Nelson & O'Connell, 1978) was 103 (101–114). When assessed just before scanning, their mean ratings on the Comprehensive Assessment of Symptoms and History (Andreasen, 1986) were: positive thought disorder, 2.5 (2–3); alogia, 0.6 (0–3); delusions, 2.0 (0–3); hallucinations, 0.8 (0–3); mania, 0.5 (0–3); depression, 0.8 (0–4); and affective flattening, 1 (0–3). After a complete description of the study to the subjects, written informed consent was obtained. The study was approved by the hospital ethical committees, and by the Administration of Radioactive Substances Advisory Committee (UK).

Eliciting thought-disordered speech

Subjects lay with their head in a PET camera, facing a Macintosh computer screen positioned approximately 25 cm from their eyes. Fifteen seconds before the onset of each scan, a picture appeared on the screen (*Persuasion*; Aldus Corp., Seattle, WA), and remained there throughout image acquisition. Pilot work had indicated that there was usually a delay of around 15 seconds between presentation and the first verbal response. Subjects were instructed to describe each picture in words ("describe the picture to me as fully as you can"), starting as soon as it appeared, and to maintain their gaze on the screen throughout the scan. Once positioned inside the camera, they had one practice trial of the task before the onset of scanning. This trial, and those used earlier during subject recruitment, involved different pictures to those used during image acquisition. Subjects spoke freely for as long as they wished; no prompting was given if they paused or stopped. A total of 12 different pictures were presented, with an interval of 10 minutes between each. The pictures were drawn from the Thematic Apperception Test (Murray, 1943), and comprised grey scale whole-body representations of people in scenes whose interpretation was ambiguous (e.g. a man standing over a person lying on a bed). They were similar with respect to their visual form and content, and had previously been found to evoke positive thought disorder in people with schizophrenia (Liddle, 1998). Each subject was presented with the same series of pictures, in the same order.

PET scanning

Regional cerebral blood flow was examined by measuring the distribution of radioactivity in the brain after the intravenous infusion of $H_2{}^{15}O$, using a CTI model 953B PET scanner with collimating septa retracted to improve sensitivity. $H_2{}^{15}O$ at a concentration of 55 MBq/ml was infused as a slow bolus through an antecubital vein at 10 ml/min. The integrated counts per pixel in the 90-second frame beginning 0–5 seconds before the rising phase of the head curve were used as an index of rCBF. The total radiation dosage per subject did not exceed 6.5 mSv effective dose equivalents. Correction for attenuation was made by performing a transmission scan with three ^{68}Ge rod sources at the beginning of each session. Images were reconstructed using three-dimensional filtered-back projection, with a ramp filter (cut-off frequency 0.5 cycles/pixel). The resolution of the resulting images was approximately $6 \times 6 \times 6$ mm full width at half maximum.

Assessment of thought disorder during scanning

Subjects were video-taped during each scan, and their speech was subsequently analysed from these recordings. Only speech produced during the rising phase of the head curve (defined as the period between the first elevation of counts above background and the peak of the head curve) of acquired counts was assessed, as measurements of rCBF made with the method employed primarily reflect activity during this 30- to 45-second period. The severity of thought disorder was evaluated using the Thought Language and Communication Index (TLCI; Liddle, 1998), by an investigator trained in its application (D.J.Q.), who was blind to the neuro-imaging results. The total score for positive TLCI items (looseness, peculiar word usage, peculiar sentence construction, peculiar logic and distractibility) was used as an index of verbal disorganisation (positive thought disorder). Perseveration and weakening of goal were not included, as their positive/negative status is unclear (Andreasen & Grove, 1986; Liddle, 1987). The total number of words articulated during the rising phase of the head curve was used as a measure of the amount of speech produced (independent of thought disorder) during each scan.

Image analysis

Images were analysed on a SPARC 20 workstation using Statistical Parametric Mapping (SPM; Wellcome Department of Cognitive Neurology, UK), implemented in Matlab. The 12 images from each subject were realigned to correct for head movement between scans, with the parameters of this rigid body transformation estimated using a least squares approach. The re-aligned images were transformed into a standard stereotactic space corresponding to the atlas of Talairach and Tournoux, by matching them to a template image (Friston *et al*, 1995). In order to increase signal to noise ratio and accommodate normal variability in functional and gyral anatomy, each image was smoothed with a 16 mm wide isotropic Gaussian kernel. Global differences in cerebral blood flow between scans, and between subjects, were covaried out, using a subject-specific ANCOVA. Significant correlations between ratings of thought disorder and rCBF were estimated on a voxel-by-voxel basis, according to the general linear model, using the rating for each scan as the covariate of interest (Friston *et al*, 1995). Possible effects owing to variations in the amount of speech produced were removed by entering the total number of words articulated during the rising phase of the head curve of each scan as an additional covariate. Voxels where the regression was significant constituted statistical parametric maps of the *t* statistic. These were transformed to the unit normal distribution permitting analysis of the group data. A threshold of $P<0.001$ (uncorrected) was employed in order to reduce the risk of Type I errors. Voxels where rCBF was correlated with the total number of words articulated per scan were also identified, to localise areas associated with speech production *per se* (independent of thought disorder).

RESULTS

Ratings of positive thought disorder

In all subjects there was a range of severities of positive thought disorder across the 12 scans (range of scores=0.0–8.0; mean score=2.4; s.d.=1.8). The pattern of responses was idiosyncratic, with no consistent relationship between the pictures and the severity of verbal disorganisation they elicited in different individuals ($F(11, 60)=0.27$, $P=0.98$).

Neural correlates of positive thought disorder

Positive thought disorder was positively correlated with rCBF in a region spanning the junction of the left parahippocampal and fusiform gyri, and in a smaller area in the anterior portion of the right fusiform gyrus ($P<0.001$, uncorrected; Table 1, Fig. 1a). Positive correlations were also seen in the body of the right caudate nucleus (Table 1). The main negative correlations were evident in an area encompassing the left inferior frontal gyrus and anterior insula, a left temporal region focused on the superior temporal gyrus, the central portion of the cingulate gyrus

Table 1 Brain regions where activity was correlated with the severity of positive thought disorder ($P<0.001$)

x	*y*	*z*	Z score	Area
Positive correlations				
18	−6	24	3.6	Right body of caudate nucleus
−30	−42	−12	3.4	Left parahippocampal/fusiform gyrus (BA 35/36)
34	−44	−20	3.4	Right fusiform gyrus (BA 37)
Negative correlations				
−42	−24	0	4.1	Left superior temporal gyrus (BA 42)
44	30	0	4.1	Right inferior frontal gyrus (BA 47)
−46	10	0	4.1	Left insula
−40	22	0	3.8	Left inferior frontal gyrus (BA 47)[1]
0	−18	40	3.7	Anterior/posterior cingulate gyrus (BA 24/31)
34	20	36	3.4	Right middle frontal gyrus (BA 9)

1. Subsidiary focus.
BA, Brodmann's area.

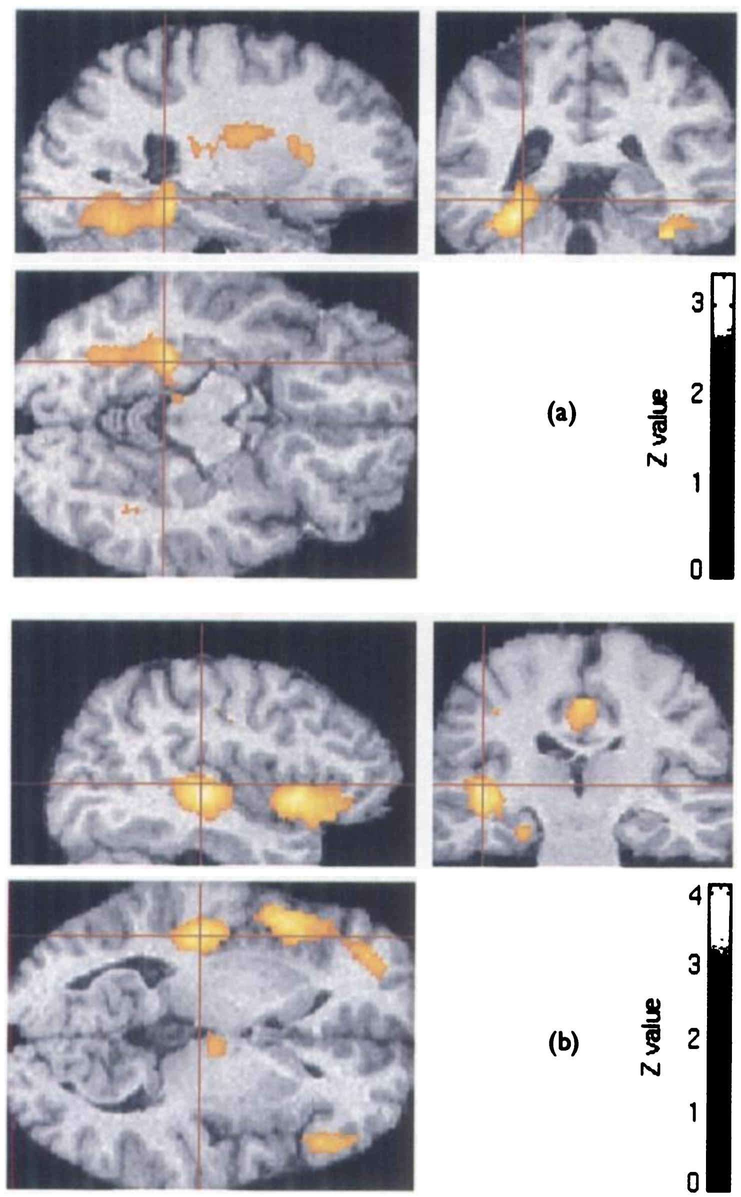

Fig. 1 Brain areas where activity was correlated with 'positive' thought disorder. The PET data have been mapped onto a normal magnetic resonance image in standard stereotactic space, sectioned to provide transverse, coronal and sagittal views. The left side of the brain is shown on the left side of the image. (a) Positive correlations between the severity of positive thought disorder and regional cerebral blood flow (rCBF) at the junction of the left parahippocampal and fusiform gyri (marked by cross hairs), and in the anterior part of the right fusiform gyrus; (b) negative correlations between positive thought disorder and rCBF in the inferior frontal and cingulate cortex, and the left superior temporal gyrus (cross hairs).

and in the right inferior frontal gyrus ($P<0.001$, uncorrected; Fig. 1b, Table 1).

Neural correlates of speech production

The total number of words articulated (independent of thought disorder) was positively correlated with activity in a left frontal region, which included the inferior frontal gyrus and the adjacent insula, and in a left temporal region focused on the superior temporal gyrus ($P<0.001$, uncorrected; Table 2). These regions were similar to sites where rCBF was negatively correlated with verbal disorganisation (above).

DISCUSSION

Method

Studies of schizophrenia are often complicated by difficulties in matching patients with healthy volunteers and the probable heterogeneity of the disorder. In the present study, we focused on a specific phenomenon within schizophrenia, and sought to measure its functional correlates as it was elicited to varying degrees in each subject. The patients thus served as their own controls, minimising the potentially confounding effects of between-subject differences in demographic variables, IQ, medication and other psychotic phenomena. The effects of differences in the amount of speech produced were removed by using the number of words per scan as a covariate in the analysis. While it is possible that the stimuli used to elicit thought disorder also evoked other phenomena, such as emotions and memories, these would only have had a confounding effect if their severity had paralleled that of verbal disorganisation.

As formal thought disorder is not evident in healthy volunteers, our study did not involve a control group. However, subtle linguistic anomalies can occur in normal speech, and it would be interesting to compare their neural correlates with those associated with thought disorder. Because the temporal resolution of PET using $^{15}O_2$ is 30–45 s, the correlations we observed reflected the presence of all the positive features of thought disorder that occurred during that period. Eliciting thought disorder in conjunction with functional magnetic resonance imaging, which has a superior temporal resolution, may permit the study of discrete linguistic anomalies.

Functional neuroimaging has not been used to examine brain activity while patients are actually producing thought-disordered speech ('on-line') before. Previous studies have involved scanning patients with schizophrenia in the resting state, and correlating this activity with ratings of 'spontaneous' (i.e. not experimentally provoked) thought disorder, made outside the scanner. This approach has linked the disorganisation syndrome (the cardinal feature of which is positive thought disorder; Liddle, 1987) with reduced resting inferior frontal activity and increased anterior cingulate activity (Liddle *et al*, 1992), and with reduced resting activity in the caudate nucleus (Ebmeier *et al*, 1993).

Negative correlations

We found that the severity of positive thought disorder was inversely correlated with activity in the inferior frontal and cingulate cortices. These regions are normally engaged when subjects select a word appropriate for a particular category (Warburton *et al*, 1996) or for the completion of a sentence (Nathaniel-James *et al*, 1997), procedures which entail the concomitant suppression of words which are inappropriate. People with schizophrenia with positive thought disorder perform poorly on such tasks (Liddle & Morris, 1991; Allen *et al*, 1993; Nathaniel-James & Frith, 1996), as do patients with frontal and cingulate lesions (Devinsky *et al*, 1995; Burgess & Shallice, 1996). The negative correlations in these regions may thus reflect a failure to engage areas which normally control the production of speech. Pathophysiological changes in these areas might also account for the association between positive thought disorder and the disorganisation of emotion and behaviour in schizophrenia (Liddle & Morris, 1991).

Partly on the basis of reports of inverse correlations between the severity of positive thought disorder and left superior temporal volume in schizophrenia (Shenton *et al*, 1992), we also predicted that the severity of verbal disorganisation would be related to activity in this region. The left superior temporal gyrus is implicated in the monitoring of one's own speech (McGuire *et al*, 1996), a process which occurs at both the pre- and post-articulatory level. Lesions of the left superior temporal region are associated with a jargon aphasia characterised by speech which is fluent but contains semantic errors (Faber *et al*, 1983), and bears some resemblance to the thought-disordered speech in schizophrenia. People with jargon aphasia also resemble patients with positive thought disorder in seeming relatively unaware of the verbal errors they produce (Harrow & Miller, 1980). Relatively reduced activity in this region might thus be associated with impaired detection of self-generated linguistic anomalies.

The negative correlations in the inferior frontal, cingulate and superior temporal cortex are remarkable, as these regions are normally activated during speech production, and are specifically implicated in the detection and correction of verbal anomalies (Devinsky *et al*, 1995; Burgess & Shallice, 1996; McGuire *et al*, 1996; Warburton *et al*, 1996; Nathaniel-James *et al*, 1997). One might therefore have expected these areas to be particularly engaged by the articulation of speech which included frank linguistic errors. However, in our subjects, the production of linguistic anomalies in thought-disordered speech was inversely correlated with activity in these regions. Moreover, these changes were specific to verbal disorganisation, as the production of speech *per se* (independent of thought disorder) in the same subjects was associated with left inferior frontal and superior temporal activation, as in healthy volunteers. This paradoxical reduction of activity in areas that normally regulate verbal output might be a key factor in the production of thought-disordered speech.

Positive correlations

Positive correlations between positive thought disorder and rCBF were evident in the parahippocampal/anterior fusiform region, particularly on the left side.

Table 2 Brain regions where activity was correlated with the amount of speech produced ($P < 0.001$)

x	*y*	*z*	Z score	Area
Positive correlations				
−36	20	0	3.7	Left insula/inferior frontal gyrus (BA 47)
−48	−12	0	3.5	Left superior temporal gyrus (BA 22)
Negative correlations				
26	−12	32	3.5	Right anterior cingulate gyrus (BA 24)

BA, Brodmann's area.

CLINICAL IMPLICATIONS

- 'Positive' thought disorder appears to involve brain areas that normally regulate and monitor speech output.
- The findings are consistent with the notion that certain features of thought disorder can be grouped together as 'positive'.
- Asking people with schizophrenia to describe ambiguous pictures can be used to elicit thought-disordered speech.

LIMITATIONS

- The temporal resolution of PET precluded correlations with discrete linguistic anomalies.
- The number of subjects was small.
- The neural correlates of the more subtle linguistic anomalies that occur in normal speech are unknown.

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Although these correlations were not predicted, data from electrophysiological, functional imaging and lesion studies indicate that this region is involved in processing the semantic features of language (McCarthy *et al*, 1995; Vandenberg *et al*, 1996), and is particularly responsive when subjects encounter unexpected stimuli, such as words anomalous with respect to the preceding context (McCarthy *et al*, 1995), or experimental perturbations of their speech while they are talking (McGuire *et al*, 1996). As thought-disordered speech is characterised by words which are incongruous with the overall meaning of what is being said, the correlations in the parahippocampal/fusiform region may have been related to the presence of self-generated anomalies within the subjects' own speech. Given that people with thought disorder appear to be relatively unaware of such errors (Harrow & Miller, 1980), this raises the intriguing possibility that they are associated with a neural response despite not being consciously perceived. The parahippocampal cortex is one of the most frequently reported sites of anatomical abnormalities in schizophrenia, but although one study has linked positive thought disorder with the volume of grey matter in this region (Chua *et al*, 1997), the relationship of such changes to specific phenomena remains unclear. In the present study, positive thought disorder was also correlated with activity in the right caudate nucleus. Although these correlations were not anticipated, involvement of the basal ganglia in thought disorder would be consistent with evidence that grammatical rules are processed by a fronto-striatal procedural system (Ullman *et al*, 1997).

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