Using the Stroop task to investigate the neural correlates of symptom change in schizophrenia

Lydia Krabbendam, Owen O’Daly, Lucy A. Morley, Jim van Os, Robin M. Murray and Sukhwinder S. Shergill

Summary
This study examined brain activation during a cognitive inhibition task in patients with schizophrenia following changes in their positive symptoms. A Stroop task was used during functional magnetic resonance imaging in 11 patients with schizophrenia (patient group) and 9 healthy volunteers (control group). At baseline, the patient group showed significantly attenuated activation within the anterior cingulate gyrus, left pre-/postcentral gyrus and inferior frontal junction. At follow-up, there was a significant increase in activation in the left inferior frontal junction associated with a decrease in positive symptoms, suggesting this region plays a role in the development of these symptoms.

Declaration of interest
None.

Reduced cognitive inhibition may contribute to the development of positive symptoms.1 The Stroop task is a classic test of cognitive inhibition, in which the processing of an irrelevant dimension of the stimuli (words) conflicts with a competing stimulus dimension (colours).2 Increased interference on the Stroop task has been demonstrated in patients with schizophrenia.3

The anterior cingulate cortex, left inferior frontal gyrus and left inferior frontal junction are the core processing areas for the Stroop interference effect in healthy individuals.4 Both the anterior cingulate and prefrontal cortex have been implicated in the increased susceptibility to the Stroop effect in schizophrenia.5,6

If positive symptoms of psychosis arise as a consequence of reduced cognitive inhibition, then symptom change will be reflected in the activation of cortical regions associated with inhibition. We hypothesised that: (a) performance on the Stroop task would be associated with attenuated activation in the anterior cingulate cortex and the left inferior frontal gyrus/junction in schizophrenia; and (b) changes in positive symptoms would be correlated with activation in these areas.

Method

We studied 11 patients (9 males) with DSM–IV7 schizophrenia: mean age, 35.4 years (s.d.=9.2); years in full-time education, 13.5 (s.d.=2.1); National Adult Reading Test (NART)8 IQ, 106.9 (s.d.=11.0); duration of illness, 12.6 years (s.d.=9.1). All were receiving stable doses of antipsychotic medication (mean chlorpromazine equivalent, 523 mg/day (s.d.=455); eight patients treated with conventional and three patients with atypical antipsychotics). The interval between baseline and follow-up was 2 years (s.d.=1.6) at baseline and 2.0 years (s.d.=0.9) at follow-up. The mean percentage error was 2.8% (s.d.=6.0). Nine healthy controls without a family history of psychosis were scanned once; complete data were not available for two people owing to technical problems in the recording of the behavioural data. Controls (four males) were comparable to patients for age (mean=33.3 years (s.d.=7.2), t(16)=–0.50, P=0.62) and education (mean=15.7 years (s.d.=3.1), t(16)=1.78, P=0.09). Mean NART score in the control group was 118.6 (s.d.=2.0) (t(16)=2.6, P=0.02).

Individuals were excluded if they had a history of drug or alcohol misuse, neurological illness, head injury, speech/hearing difficulty or any contraindication to magnetic resonance imaging (MRI) scanning such as metal implants. All participants provided informed consent; ethical approval was provided by the Institute of Psychiatry ethics committee.

The Stroop task consisted of congruent, incongruent, neutral and baseline (fixation cross) conditions. The analysis contrasted the incongruent condition (colour name printed in an incongruent colour) with the congruent condition (colour name printed in the congruent colour). Participants were presented with a stimulus every 6 s, named the colour of the word in a 4 s quiet period which was followed by 2 s of compressed sequence acquisition. There were 20 trials for each condition, resulting in a total of 80 trials, presented in random order suitable for an event-related analysis.

Data were acquired at 1.5 T and analysed using XBAM (www.brainmap.it) with protocols previously described10 (see online supplement).

Results

A two × two ANOVA comparing error rates between groups (patients v. controls) and conditions (congruent v. incongruent) revealed a trend main effect of condition (F(1,16)=3.59, P=0.07; congruent: 4.4% (s.d.=7.0); congruent: 1.1% (s.d.=2.1)). There was no significant main effect of group (F(1,16)=0.06, P=0.80; controls: 2.5% (s.d.=5.8); patients: 3.0% (s.d.=5.3)). At follow-up, the mean percentage error was 2.8% (s.d.=6.0).

Controls demonstrated a significant increase within the left pre-/postcentral gyrus, extending into the left inferior frontal gyrus, the anterior cingulate cortex and the left lingual gyrus during the incongruent compared with the congruent condition. The patient group showed significantly attenuated activation within the left pre-/postcentral gyrus extending into the left
inferior frontal junction, the anterior cingulate cortex and the right middle temporal gyrus (online Fig. D5a) during the incongruent condition compared with controls.

Although there was increased activation in the bilateral pre-/postcentral gyrus extending into the left inferior frontal junction during both incongruent and congruent conditions at follow-up, only inferior frontal junction activation was specific to the incongruent condition (online Fig. D5b) and correlated with reduced positive symptoms (Pearson’s $r=0.89$, $P<0.01$) (online Fig. D5c).

**Discussion**

In controls, the areas activated show substantial overlap with a recent meta-analysis of imaging findings in the Stroop task for the left inferior frontal junction/gyrus and the anterior cingulate cortex. The finding of attenuated anterior cingulate cortex activation in patients replicates previous results but our study suggests that the left inferior frontal junction is also implicated. Recent Stroop studies have suggested that inferior frontal junction/gyrus and anterior cingulate cortex are related to top-down control and conflict detection respectively. The task-junction/gyrus and anterior cingulate cortex are related to top-down control and conflict detection respectively. The task-related attenuation in the inferior frontal junction/gyrus in patients suggests that prefrontally mediated implementation of top-down control is compromised in schizophrenia, consistent with a long tradition of studies reporting abnormal prefrontal functioning in this disorder. The results suggest that normalisation of the task-related activity in this area may contribute to the reduction of positive symptoms of psychosis, possibly through a reduced susceptibility to interference. As Stroop interference may be specifically related to effects of disorganisation, future studies could test whether the observed association between signal change and decrease in positive symptoms can be accounted for by specific items within the positive symptom domain.

Methodological limitations include first, the issue of generalisability and specificity of the results from the analysis of a relatively small number of participants and experimental trials. However, we used established non-parametric image analysis software with stringent thresholds to minimise any Type I errors. Second, use of medication in the patient group may have influenced 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. Patients did not have any alterations in their antipsychotic medication between the two imaging sessions, thus findings are unlikely to be related to changes in medication. Third, we did not examine reaction time differences in participants, as subtle variation in reaction time is unlikely to influence the rather slow blood oxygen level dependent response measured by functional MRI. However, it would be interesting to investigate the influence of reaction time in future studies.

Finally, repetition effects of the task may confound these findings; however, a passive auditory and visual stimulation experiment showed no changes between the two scans, excluding any non-specific repetition or session effects and we observed a significant correlation between the increased activation in the inferior frontal junction and the reduction in positive symptoms.

It would be interesting to examine the effects on positive symptoms of increasing the inferior frontal junction, or prefrontal, activation on positive symptoms through specific interventions using either pharmacological, neurofeedback or psychological techniques.

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**References**

Data supplement

Functional magnetic resonance imaging

Data acquisition
Data were acquired using a 1.5 T GE Signa Neuro-optimised MR System (GE, Milwaukee, Wisconsin, USA) at the Maudsley Hospital, London. A quadrature birdcage head coil was used for radio frequency transmission and reception. One hundred $T_2^*$-weighted gradient echo-planar images depicting blood oxygen 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 mm, 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 magnetic resonance 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.1

Image analysis
Movement estimation and correction procedures as described by Friston et al2 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.3 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 (SSQ) due 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 ten 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 functional MRI time series analyses and shown to give excellent Type I error control.4 Statistical testing at group level was carried out after transformation of the SSQ ratio maps obtained from the observed and randomised data into standard space.5 Median activation maps were computed across participants 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 statistics6 and random permutation of group membership to obtain the distribution of SSQ ratio 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 follow-up, we examined the main effects of time and difficulty and extracted the mean SSQ from the regional clusters showing a difference over time and examined these for correlations with change in the PANSS positive subscale.

References
Fig DS1 (a) Differential activation in controls compared with patients during the incongruent condition of the Stroop task. In patients, attenuated activation in the anterior cingulate gyrus (Talairach coordinates: x=0, y=-7, z=42), the left inferior frontal junction (-43, 7, 31), the left pre-/postcentral gyrus (-51, -15, 37) and the right middle temporal gyrus (58, -26, 7) was seen. (b) Changes in cortical activation from baseline to follow-up in patients during the incongruent condition of the Stroop task. Greater activation was seen at baseline in the right postcentral gyrus (54, -7, 15), whereas the left inferior frontal junction (-36, 4, 31) and the pre-/postcentral gyrus (51, -15, 37) bilaterally were more active at follow-up. Clusters in blue demonstrate greater activation at baseline, and clusters in yellow/orange show greater activation at follow-up. (c) Graph plotting the changes in activations in the left inferior frontal junction (-36, 4, 31) as a function of reduction in positive symptoms from baseline to follow-up. Left hemisphere appears to the right of the page. Lines on sagittal slices correspond to the orientation of the axial slices.
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Supplementary Material
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