

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 al*² 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

- 1 Talairach J, Tournoux P. *Co-Planar Stereotaxic Atlas of the Human Brain*. Thieme Medical, 1988.
- 2 Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R. Movement-related effects in fMRI time-series. *Magn Reson Med* 1996; **35**: 346–55.
- 3 Friston KJ, Josephs O, Rees G, Turner R. Nonlinear event-related responses in fMRI. *Magn Reson Med* 1998; **39**: 41–52.
- 4 Bullmore E, Long C, Suckling J, Fadili J, Calvert G, Zelaya F, et al. Colored noise and computational inference in neurophysiological (fMRI) time series analysis: resampling methods in time and wavelet domains. *Hum Brain Mapp* 2001; **12**: 61–78.
- 5 Brammer MJ, Bullmore ET, Simmons A, Williams SC, Grasby PM, Howard RJ, et al. Generic brain activation mapping in functional magnetic resonance imaging: a nonparametric approach. *Magn Reson Imaging* 1997; **15**: 763–70.
- 6 Bullmore ET, Suckling J, Overmeyer S, Rabe-Hesketh S, Taylor E, Brammer MJ. Global, voxel, and cluster tests, by theory and permutation, for a difference between two groups of structural MR images of the brain. *IEEE Trans Med Imaging* 1999; **18**: 32–42.

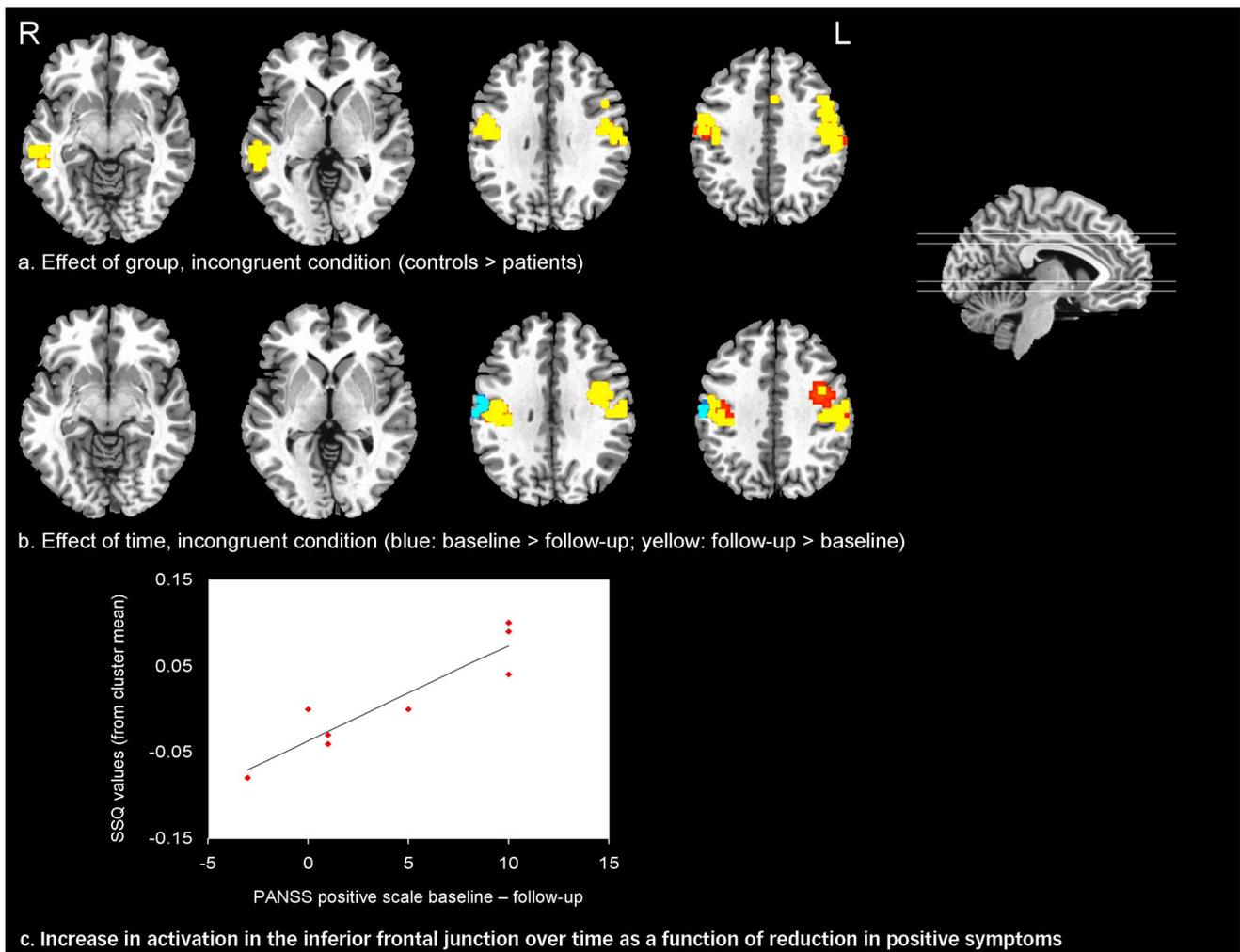


Fig. DS1 (a) Differential activation in controls compared with patients during the incongruent condition of the Stroop task. In patients, attenuated activation in the anterior cingulate gyrus (Talairach coordinates: $x=0$, $y=7$, $z=42$), the left inferior frontal junction (-43 , 7 , 31), the left pre-/postcentral 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.