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Online supplement

Data acquisition

Data were acquired using a 1.5 T GE Signa neuro-optimised magnetic resonance system (General Electric, Milwaukee, Wisconsin, USA) at the Maudsley Hospital, London. A quadrature birdcage head coil was used for radiofrequency transmission and reception. Two hundred and forty T_2*-weighted gradient echo planar images depicting blood oxygen level-dependent (BOLD) contrast were acquired from 16 non-contiguous planes parallel to the anterior commissure-posterior commissure plane: slice thickness 7.7 mm, slice gap 0.7 mm, repetition time (TR) 2 s, echo time (TE) 40 ms, flip angle 90°. 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 & Tournoux.[1]

Image analysis

Data were analysed with software developed at the Institute of Psychiatry, London, using a non-parametric approach (for a full description and references see http://www.brainmap.it). Experimental responses were analysed by convolving each component of the experimental design with each of two gamma variate functions (peak responses at 4 s and 8 s respectively). The best fit between the weighted sum of these convolutions and the time series at each voxel was computed using the constrained BOLD effect model of Friman *et al*.[2] Following computation of the model fit, a goodness of fit statistic was computed. This consisted of the ratio of the sum of squares of deviations from the mean image intensity (over the whole time series) due to the model to the sum of squares of deviations due to the residuals (SSQ ratio). Following computation of the observed SSQ ratio at each voxel, the data were permuted by the wavelet-based method,[3] from which activation of voxels and clusters can be detected at any desired type 1 error rate.[4] In addition to the SSQ ratio, the size of the BOLD response to each experimental condition was computed for each individual at each voxel as a percentage of the mean resting image.

Within-group comparisons of experimental conditions to each contrast of interest were then computed separately for the patient and the control group. The observed and permuted SSQ ratio maps for each individual, as well as the BOLD effect size maps, were transformed into standard space[1] using the two-stage warping procedure.[5] Cluster level maps are thresholded at <1 expected type I error cluster per brain. Group activation maps were then computed by determining the median SSQ ratio at each voxel (over all individuals) in the observed and permuted data maps (medians are used to minimise outlier effects). The distribution of median SSQ ratios over all intracerebral voxels from the permuted data were then used to derive the null distribution of SSQ ratios, which can be thresholded to produce group activation maps at any desired voxel or cluster-level type 1 error rate. In the two-level clustering procedure,[4] the first (voxelwise) thresholding is carried out with an uncorrected P value of 0.05 to give the maximum allowable sensitivity. In order to eliminate the resulting false positive activations, a second, cluster-level thresholding step is carried out, and the threshold of this second step is adjusted to give an expectation of less than one false positive cluster over the whole brain. As the cluster level threshold is set at the whole brain level, the normal, voxelwise issue of multiple comparisons does not apply.

Comparisons of responses between groups or experimental conditions was performed using non-parametric analysis of variance (ANOVA). Data were fitted at each intracerebral voxel at which all participants have non-zero data using a linear model of the type $Y = a + bX + e$, where Y is the vector of BOLD effect sizes for each individual, X is the contrast matrix for the particular intercondition/group contrasts required, a is the mean effect across all individuals in the various condition/group, b is the computed group/condition difference and e is the vector of residual errors. The model is fitted by minimising the sum of absolute deviations rather than the sums of squares to reduce outlier effects. The null distribution of b is computed by permuting data between conditions (assuming the null hypothesis of no effect of experimental condition or group membership) and refitting the above model. Group difference maps are computed as described above at voxel or cluster level by appropriate thresholding of the null distribution of b, to give less than one false positive cluster per image. This is a standard method for tests of this kind and it gives exact P values with minimum assumptions.[6]

References

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