**Supplementary material**

**MRI methods**

**MRI acquisition parameters:** The image acquisition was performed on a 3T Philips Achieva MR system (Philips Medical Systems, Best, The Netherlands) equipped with gradient strength 80 mT/m and slew rate 200 T/m/s using an 8-channel receive-only head coil, in the Centre for Advanced Medical Imaging (CAMI), St. James’s Hospital.  A 3D Inversion Recovery prepared Spoiled Gradient Recalled echo (IR-SPGR) sequence was used to obtain high resolution T1-weighted images of the brain, with: FOV =  256 x 256 x 160 mm3, spatial resolution 1 mm3, TR/TE = 8.5/3.9 ms, TI =1060 ms, flip angle = 8°, SENSE factor = 1.5, acquisition time = 7 min 30 s.

N-back fMRI data were acquired using a SE-EPI sequence with a dynamic scan time of 2 s, with:  FOV = 240 x 240 x 132 mm, spatial resolution = 3 x 3 x 3.2 mm, 38 slices with interslice gap = 0.3 mm, TR/TE = 2000 / 28 ms, SENSE factor = 2, with SPIR fat suppression and dynamic stabilisation.  In total, 126 dynamic scans were acquired for the N-back task in an acquisition time of 4 min 12 s.

Resting-state fMRI data were acquired using the same SE-EPI sequence, with an acquisition time of 7 minutes (210 dynamic scans).

**N-back paradigm:** During the N-back task, participants watched a series of numbers between 1 and 4 which were presented on a computer screen (participants watched this computer screen reflected in a mirror during the scan) (Callicott et al., 2000).  During the 0-back condition (the control condition), participants had to press a button corresponding to the number presented on the screen.  In the 2-back working memory condition, participants had to press a button corresponding to the number seen two numbers before the presented number.  Four blocks were presented of each condition, and the task alternated between 0-back and 2-back.   Behavioural measures included accuracy (number of correct responses out of 108) and reaction time (in ms).

**Resting-state:** During the resting-state scan, participants were instructed to keep their fixation on a fixation cross presented on the screen for 7 minutes.

**MRI spatial preprocessing:** Both N-back and resting-state preprocessing followed the same procedure. Spatial pre-processing was carried out using Statistical Parametric Mapping (SPM8, v6313, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) and MATLAB R2014a (v8.3.0.532; http://www.mathworks.co.uk/). Functional images were realigned to the mean image to reduce the effects of motion. The T1 structural image was then co-registered to the mean functional image for more precise spatial normalisation. The realigned functional images were normalised to MNI (Montreal Neurological Institute) space using the unified segmentation approach with a voxel size of 2 × 2 × 2 mm3 (Ashburner and Friston, 2005) and then smoothed with an 8 mm FWHM (full width at half maximum) isotropic Gaussian filter. Artefact detection was performed using the Artefact Detection Tools (ART) toolbox (http://www.nitrc.org/projects/artifact\_detect/). Pre-processed images showing variations in global mean intensity greater than 3 standard deviations, and/or composite motion greater than 1 mm, were considered outliers (Whitfield-Gabrieli, S., personal correspondence) and entered as regressors of no interest in each individual’s first level general linear model (or in the case of resting-state fMRI data into their subsequent CONN toolbox analysis).

**N-back fMRI statistical analsysis:** Statistical analysis was performed using the general linear model (GLM) (Friston et al., 1994) and a contrast of 2-back > 0-back. Individual contrast maps produced by this analysis were entered into a second-level random effects analysis to examine group x time interactions – a flexible factorial model in SPM8 with factors subject (variance set to equal, independence set to yes), group (variance set to unequal, independence set to yes) and time (variance set to equal, independence set to no) (Glascher and Gitelman, 2008). Statistical significance was set at p < 0.001 (uncorrected) and clusters were considered statistically significant at a p < 0.05, family-wise error (FWE) corrected for multiple comparisons across the whole brain at the cluster level. Anatomical locations of peak coordinates of significant clusters were identified using the Anatomy\_v22c\_MPM atlas within the Anatomy Toolbox (Version 2.2b) in SPM8 (Eickhoff et al., 2005; Eickhoff et al., 2006; Eickhoff et al., 2007).

**Resting-state functional connectivity analysis:** Resting-state fMRI data were analysed using the CONN toolbox (v15; National Institutes of Health Blueprint for Neuroscience Research [https://www.nitrc.org/projects/conn]). Data were temporally band-pass filtered (range: 0.008 - 0.09 Hz), and effects of motion and signals from white matter and cerebrospinal fluid were removed using linear regression (Whitfield-Gabrieli and Nieto-Castanon, 2012).

Based on a previous resting-state fMRI study from our group (Mothersill et al., Under Review), we examined functional connectivity within the default network, affective network, and ventral attention network, as we previously identified significant differences in functional connectivity of these networks in patients with schizophrenia compared to healthy controls. This involved examining functional connectivity of the following seed regions-of-interest (ROIs) where we previously observed effects: left precuneus, right precuneus, left anterior cingulate cortex and left temporoparietal junction. In addition, we examined the cognitive control network due to the putative importance of this network in working memory training (left and right dorsolateral prefrontal cortex seed ROIs). Functional connectivity maps of Fisher-transformed correlation coefficients were computed by extracting the mean BOLD time-series separately from each seed ROI and correlating this time-series with the time series of all other voxels in the brain.

Seed ROIs were made up of spheres of 5 mm radius centered on the coordinates of interest from each network (McCarthy et al., 2013; Mothersill et al., Under Review). Coordinates of interest were taken from previous resting-state fMRI studies (Fox et al., 2006; Sheline et al., 2010). Where coordinates were presented in Talaraich space, they were converted to MNI space using GingerALE 2.3 (‘Talairach to MNI (SPM)’ transform) (Eickhoff et al., 2009; Turkeltaub et al., 2012). The Wake Forest University Pickatlas was then used to create ROIs as masks (Maldjian et al., 2003; Maldjian et al., 2004; Tzourio-Mazoyer et al., 2002). Networks and the coordinates of the associated seed regions are presented in **Supp Table 1**.

The functional connectivity maps for each seed region that was created by CONN (BETA\_Subject\*.nii files) were then entered into a flexible factorial model to examine group x time interactions (see above). Statistical significance was set at p < 0.001 (uncorrected) and clusters were considered statistically significant at a p < 0.00125 level, family-wise error (FWE) corrected for multiple comparisons across the whole brain at the cluster level. This was reduced from 0.05 due to examination of functional connectivity across four separate resting-state networks, following previous studies by our group (McCarthy et al., 2013; Mothersill et al., Under Review).

**Supplementary Table 1 –** Resting-state networks and associated seed coordinates in MNI space

|  |  |
| --- | --- |
| **Network** | **Seed coordinates (x y z)** |
| Default mode network (precuneus) | ±9 -60 25 |
| Cognitive control network (DLPFC) | ±40 33 24 |
| Affective network (ACC) | -12 39 -11 |
| Ventral attention network (TPJ) | -59 -47 22 |

DLPFC = dorsolateral prefrontal cortex; ACC = anterior cingulate cortex; TPJ = temporo-parietal junction

**Supplementary Table 2 –** N-back fMRI participant demographics

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Mean age in years (s.d.a) | Gender (M:F) | IQ at time 0 (s.d.) | 2-back accuracy at time 0 (s.d.) | 2-back reaction time  (in ms) at time 0 (s.d.) | Mean ART outliers T0 (s.d.) | Mean ART outliers T1 (s.d.) |
| CR patients  (n = 14) | 45.57 (12.28) | 8:6 | 96.14 (18.33) | 71.21 (25.89) | 7569.07 (1658.05) | 11.14 (11.77) | 7.86 (9.83) |
| Control patients  (n = 15) | 43.27(11.32) | 7:8 | 94.80 (22.04) | 72.67(15.04) | 6857.48 (1685.05) | 15.00 (17.97) | 10.00 (12.81) |
| Statisticb | t = 0.525957 | χ2 = 0.318277 | t = 0.177709 | t = 0.186340 | t = 1.145194 | F = 0.356251 | |
| p value | 0.603212 | 0.715249 | 0.860278 | 0.853571 | 0.262179 | 0.555568 | |

as.d. = standard deviation

b t statistic derived from an independent t-test between groups; χ2 value derived from Pearson’s chi-squared test with variables group and gender; F values correspond to a time x group interaction performed using a repeated measures ANOVA in SPSS with within-subject factor time (two levels) and mean ART outliers as measure.

**Supplementary Table 3** – N-back performance in CRT and control patients at time 1

|  |  |  |
| --- | --- | --- |
|  | 2-back accuracy at time 1 (s.d.) | 2-back reaction time at time 1 (in ms) (s.d.) |
| CR patients  (n = 14) | 77.64 (23.18) | 7061.51 (1185.38) |
| Control patients  (n = 15) | 73.47 (19.88) | 6619.06 (1468.53) |
| ANCOVA Statistic | F = 4.16 | F = 41.62 |
| P value | 0.052 | <0.001 |

as.d. = standard deviation

**Supplementary Table 4 –** Resting-state fMRI participant demographics

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Mean translation T0 (s.d.) (mm) | Mean translation T1 (s.d.) (mm) | Mean rotation T0 (s.d.) (radians) | Mean rotation T1 (s.d.) (radians) | Mean ART outliers T0 (s.d.) | Mean ART outliers T1 (s.d.) |
| CR patients (n = 12) | 0.08 (0.06) | 0.08 (0.04) | <0.01 (<0.01) | <0.01 (<0.01) | 15.92 (22.66) | 16.00 (15.56) |
| Control patients  (n = 15) | 0.07 (0.04) | 0.07 (0.04) | <0.01 (<0.01) | <0.01 (<0.01) | 15.93 (18.73) | 16.67 (17.62) |
| Statistic | F = 0.211688 | | F = 0.380941 | | F = 0.006315 | |
| p-value | 0.649424 | | 0.542681 | | 0.937292 | |

s.d. = standard deviation; F values correspond to a time x group interaction performed using a repeated measures ANOVA in SPSS with within-subject factor time (two levels) and mean translation, mean rotation and mean ART outliers as measures.

**Supplementary Table 5 –** Clusters, including individual peaks, showing CR group x time interactions on functional connectivity during rest, FWE-corrected across the whole brain at the cluster level

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Seed region** | **Extent (voxels)** | **p value** | **Cluster peak** | **t-value** | **Z-value** | **Peak (MNI)** |
| Right precuneus | 321 | 0.002 | Inferior parietal lobule | 6.53 | 4.94 | -50 -48 36 |
|  |  |  | Not found on any probability map | 5.25 | 4.27 | -62 -48 44 |
| Left anterior cingulate cortex | 189 | 0.024 | Midcingulate cortex | 4.62 | 3.89 | 12 -12 42 |
|  |  |  | Not found on any probability map | 4.41 | 3.76 | 18 -2 40 |
|  |  |  | Midcingulate cortex | 4.10 | 3.55 | 8 -4 40 |