Brain Effects of Cognitive Remediation Therapy in Schizophrenia: A Structural and Functional Neuroimaging Study

Supplemental Information

**Figure S1.** Flowchart of the randomized trial of cognitive remediation therapy for schizophrenia. MRI, magnetic resonance imaging.
The study was carried out in accordance with Declaration of Helsinki and was approved by the local research ethics committee of our university hospital. All patients signed written informed consent agreements following detailed explanation of the study and procedure.

**Tensorial Independent Component Analysis**

**T0-Baseline Cross-Sectional Analysis**

Decomposition of the fMRI data set at baseline resulted in 22 independent components (ICs). The following criteria were used to eliminate biologically irrelevant independent components using data from both patient and control groups: 1) those which did not show a consistent effect across the group because their standardized subject scores were likely to be driven by outliers, and 2) those representing known artifacts such as motion, high frequency noise or venous pulsation (1). The remaining ICs (9) were then sorted according to their mean response amplitude, which were based on the post-hoc analysis performed by MELODIC on the time series: IC1, IC2, IC3, IC6, IC7, and IC9 were categorized as working memory (WM)-related components, representing the specific task-positive network for the defined n back task, which was significant for 2 back > rest; 2 back > 0 back; 0 back > rest contrasts at \( p < .00001 \). IC4, IC5, and IC8 were sorted as rest-related components because their time course fitted the time series task and were significant for the rest > 0 back, rest > 2 back and 0 back > 2 back contrasts at \( p < .00001 \). The ICs maps (spatial localization of activation and deactivation) were also compared with those reported in the WM literature (2) and the default mode network (DMN) literature (3,4). Components with no temporal association with the task, or components related to non-cognitive networks commonly found in resting analysis were not considered (IC7).
Finally, in accordance with the subject-mode vector, significant differences in the relative activation strength between patients and controls were observed in the IC1 ($F = 158.40, p < .00001$) and IC8 ($F = 83.35, p < .00001$). Specifically, compared with the healthy control (HC) group, the cognitive remediation therapy (CRT) group showed increased activation/deactivation pattern in the task-positive network IC1-CEN ($z = 1.69, p < .04$), in which the time course fitted the time series task; $F = 425.14$ and $p < .00001$ and was significant for the 2 back $>$ 0 back contrast ($z = 10.03, p < .00001$), the 2 back $>$ rest contrast ($z = 21.37, p < .00001$), and 0 back $>$ rest ($z = 16.46, p < .00001$). At baseline, the CRT group also showed increased IC8-DMN rest related network when compared with the social skills training (SST) group ($z = 1.76, p < .03$). IC8 time course fitted the time series task, $F = 203.47, p < .00001$, and was significant for the rest $>$ 0 back contrast ($z = 17.40, p < .00001$) and rest $>$ 2 back contrast ($z = 13.15, p < .00001$).

**TI-End Point Cross-Sectional Analysis**

As time modes fitted with the time courses of their own tasks, both IC1 and also IC3 were considered WM-related components. Similarly, IC2 and IC5 were sorted as rest-related components. All those spatial maps of activation and deactivation have been previously described in the literature (2-4). Considering the subject mode vector, any statistically differences were found between groups in the different ICs. The lack of differences between the experimental group and the healthy control group at the endpoint of the study could be reinforcing the idea of a putative normalization of over-activation/deactivation pattern that was observed at baseline. As aforementioned, IC1-CEN time course fitted with the time series task ($F = 362.16; p < .00001$) and it was found to be statistically significant for the following contrasts: 2 back $>$ 0 back ($z = 10.40, p < .00001$), 2 back $>$ rest ($z = 20.48, p < .00001$) and 0 back $>$ rest ($z = 14.89, p < .00001$). In the same way, IC2-DMN time course fitted with the time series task ($F = 373.59; p < .00001$), being statistically significant not
only for rest > 0 back \((z = 16.98, p < .00001)\) but also for rest > 2 back \((z = 20.35, p < .00001)\) contrasts.

Regarding subjects-mode vector, any significant differences between groups emerged for IC1-CEN task-related activations in any of their components including left superior parietal lobe, left precentral gyrus and right middle frontal gyrus. Also, any differences appeared on task-related deactivations on posterior cingulate, right anterior cingulate and left middle temporal gyrus: HC > CRT \((z = -0.41, p < .65)\); CRT > HC \((z = 0.41, p < .34)\); CRT > SST: \((z = 0.24, p < .41)\); SST > CRT \((z = -0.24, p < .59)\). In addition, no significant differences between groups were found at the IC2-DMN rest-related activation on the left precuneus, left middle temporal gyrus, right superior parietal lobe and right lingual gyrus: HC > CRT \((z = -0.20, p < .42)\); CRT > HC \((z = 0.20, p < .52)\); CRT > SST \((z = 0.55, p < .29)\); SST > CRT \((z = -0.55, p < .79)\).

**Longitudinal Analysis**

Following the selection criteria described above, IC1, IC3, IC5 and IC8 were considered WM-related components, and IC2 was sorted as a rest-related component because its time mode fitted with the time course task, and its spatial maps (activation and deactivation) corroborated with the literature. Also in accordance with the subject mode vector, significant differences were found within the CRT group in IC1-task related activation \((F = 168.98 \text{ and } p < .00001)\) and IC2 rest-related activation \((F = 137.70 \text{ and } p < .00001)\). Compared with the baseline, IC1-CEN subject mode showed decreased activation/deactivation in post-treatment, which was significant for the T0-baseline > T1-post-treatment \((z = 2.89, p < .001)\) contrast. IC1 time course fitted with the time series task, \(F = 335.07\) and \(p < .00001\), and was significant for the 2 back > 0 back contrast \((z = 10.03, p < .00001)\), 2 back > rest \((z = 21.37, p < .00001)\) and 0 back > rest \((z = 16.46, p < .00001)\).
Compared with baseline, IC2-DMN subject mode revealed decreased activation/deactivation in post-treatment in the CRT group, as evidenced by a significant T0-baseline \( > \) T1-post-treatment contrast \((z = 2.15, p < .015)\). IC2 time course fitted the task, \( F = 405.86, p = .000001 \), and was significant for the contrast: rest \( > \) 0 back \((z = 19.09, p < .000001)\), and rest \( > \) 2 back \((z = 20.71, p < .000001)\).

Additionally, when the pattern of changes between CRT and SST groups were compared, the CRT group showed decreased IC1-CEN activation \((F = 128.69, p = .00001)\). IC1 time course fitted the task, \( F = 335.07 \) and \( p = .000001 \), and was significant for the 2 back \( > \) 0 back \((z = 10.51, p < .00001)\), 2 back \( > \) rest \((z = 20.04, p < .00001)\), and 0 back \( > \) rest \((z = 14.15, p < .00001)\) contrasts.

**Head Movement Correction**

To introduce a head movement correction the mean of displacement (mm) was calculated. Subsequently, a one-factor analysis of variance was applied to test the significance of between-group differences. No differences at baseline were found in the mean of displacement \((F = 0.032, df = 2.42, p = .969)\) between HC \((\text{mean} = 1.126667, \text{SD} = .2537903)\), CRT \((\text{mean} = 1.148867, \text{SD} = .4750255)\) and SST \((\text{mean} = 1.113200, \text{SD} = .4131178)\). The same analysis was carried out at the endpoint and no significant differences were found \((F = 0.534, df = 2.42, p = .590)\) regarding the mean of displacement between HC \((\text{mean} = 1.091333, \text{SD} = .2534862)\), CRT \((\text{mean} = 1.218133, \text{SD} = .4226084)\) and SST \((\text{mean} = 1.110867, \text{SD} = .3870790)\). Furthermore, prior to the diffusion tensor imaging analysis, we carried out a visual inspection of the files with the images (.png) in order to check whether any volumes showed severe displacement. No differences were found. Regarding the fMRI data, we were not able to perform any statistical analysis. Nonetheless, we used the MOCO
series with intra-run motion correction produced by the scanner (3T Tim Trio Scanner. Siemens, Erlangen, Germany).

**Figure S2.** Diffusion tensor imaging analysis showing a significant increase of fractional anisotropy (red) in the genu and body of the corpus callosum in patients after cognitive remediation therapy treatment ($p < .05$ family-wise error).
Supplemental References


