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Increased activation in Broca's area after cognitive remediation in schizophrenia

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ABSTRACT

Functional magnetic resonance imaging (fMRI) was used to measure changes in cerebral activity in patients with schizophrenia after participation in the *Cognitive Remediation Program for Schizophrenia and other related disorders* (RECOS). As RECOS therapists make use of problem-solving and verbal mediation techniques, known to be beneficial in the rehabilitation of dysexecutive syndromes, we expected an increased activation of frontal areas after remediation. Executive functioning and cerebral activation during a covert verbal fluency task were measured in eight patients with schizophrenia before (T1) and after (T2) 14 weeks of RECOS therapy. The same measures were recorded in eight patients with schizophrenia who did not participate in RECOS at the same intervals of time (TAU group). Increased activation in Broca's area, as well as improvements in performance of executive/frontal tasks, was observed after cognitive training. Metacognitive techniques of verbalization are hypothesized to be the main factor underlying the brain changes observed in the present study.

1. Introduction

Cognitive deficits are a core feature in schizophrenia affecting up to 80% of patients and are associated with frontal lobe abnormalities (Medalia and Choi, 2009). Cognitive remediation programs have been designed to treat patients with these deficits and consequently to improve their functional outcome. Given the great variability of encountered deficits, the *Cognitive Remediation Program for Schizophrenia and other related disorders* (RECOS) offer specific training modules designed to target cognitive functions in a personalized way (Vianin, 2013). The RECOS program involves therapists who work with one person at a time using both paper/pencil tasks and a set of interactive computer exercises. As frontal/executive functions play a major role in the coordination of cognitive processes, RECOS therapists make use of remediation techniques developed for treating patients with frontal lesions.

The RECOS program emphasizes on problem-solving training (D'Zurilla and Nezu, 2007) and verbal mediation techniques (Franck et al., 2013; Vianin, 2013). Problem-solving strategies have proved to be effective for several psychiatric disorders, especially from a short-term psychotherapy treatment perspective (Mynors-Wallis, 2001). This technique consists of exploring a wide set of possible strategies and selecting those that turn out to be the most relevant. During paper/pencil tasks, participants are prompted to (1) define the problem, that is, to express both the targeted objectives and the obstacles to achieving them; (2) suggest different strategies to solve the problem; (3) examine, compare and possibly adjust the various strategies; and (4) apply the chosen strategy. Therapists guide participants at an individualized pace through a varied proportion of paper/pencil and computer exercises.

During cognitive training, RECOS therapists also encourage the systematic use of verbalization, as formalized by Vermersch (1994). For the participant, this metacognitive technique consists in verbalizing his/her own problem-solving strategies during the training exercises (*current verbalization*) or at the end of the session (*retrospective verbalization*). Because the participant is more attentive to the cognitive task when his/her eyes are focused on the screen, verbalization is preferentially suggested by the therapist during computer exercises. This technique has several advantages. First it allows the participants to become aware of their problem-solving strategies and to generate new ones if they

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did not succeed in the task. Secondly, it allows the therapist to observe biases of reasoning. Finally, by asking the participants to verbalize, it improves their ability to find the words to express their way of thinking. Harvey et al. (2009) showed that verbalizing ongoing actions was an effective method to enhance performance on difficult tasks among people with schizophrenia.

In a previous study (Deppen et al., 2011), we showed that patients with schizophrenia who participated in the RECOS program improved their cognitive performance in the Color-Word Stroop Test, the Wisconsin Card Sorting Test (WCST), and the Matrix Reasoning Test. We therefore hypothesized that our therapy targets executive functions and that the underlying mechanism for such improvement may be localized in frontal areas.

Only a very few studies showed increased activation of frontal areas after cognitive remediation therapy. In particular, Wykes et al. study (2002) showed increased activation in regions associated with working memory (e.g., prefrontal cortex) during an n-back task in which the participants had to identify whether a visually presented letter had appeared before. In addition, Wexler et al. (2000) observed increased task-related activation of the left inferior frontal cortex after verbal memory training. More recently, Bor et al. (2011) showed an over-activation in Broca's area in patients with schizophrenia after cognitive remediation within a verbal as well as a spatial working memory task. The authors suggested that this could be explained by the use of language functions by the participants.

In this context, the present study evaluated the effect of RECOS therapy on the activation of frontal areas during a covert verbal fluency task. As verbal fluency requires the retrieval of words from memory storage, we assume that it may identify the effect of verbal mediation techniques on frontal brain areas. Numerous functional magnetic resonance imaging (fMRI) studies showed that covert letter verbal fluency is mainly associated with the left frontal cortex, corresponding to Broca's area in healthy subjects (McGraw et al., 2001). Compared with healthy controls, individuals with schizophrenia showed a lower level of frontal response during a covert verbal fluency task (Yurgelun-Todd et al., 1996; Weiss et al., 2004). We expected therefore that verbal mediation techniques should lead to an increased activation of Broca's area and a better level of executive functioning after cognitive training.

2. Material and methods

2.1. Study design

We carried out a single blind, randomized trial of cognitive remediation therapy (RECOS) by comparing a group receiving 14 weeks of executive function training with a group who received only usual treatment without any cognitive training (TAU). We tested whether more frontal activation was observed after RECOS therapy and whether executive functioning improved in the intervention group. Cerebral activation during a covert verbal fluency task, cognitive functioning performance, and data on symptoms from the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) were recorded at pretreatment assessment (T1). After T1, participants were randomized to either RECOS or TAU. Cerebral activation during a similar verbal fluency task and performance in executive functioning were measured again 6 months later (post-therapy – T2). The remediation phase included 28 1-h sessions twice a week in a one-to-one approach and 14 h of exercises at home.

2.2. Population (see Table 1)

The study included 16 right-handed patients. They fulfilled the DSM-IV-TR (American Psychiatric Association, 2000) criteria for schizophrenia. Patients with histories of traumatic brain injury, epilepsy, alcohol and substance abuse, or other diagnosed neurological conditions were excluded from the study. All the patients were clinically stable (the participants had a score between 8 and 24 on the PANSS positive syndrome subscale). One patient in the RECOS group and one patient in the TAU group did not receive any medication during the whole study. The other patients received atypical antipsychotic medication. Medication did not vary between the first session and the second session. Patients treated with antidepressants, benzodiazepines or mood stabilizers were excluded.

2.3. Cognitive assessment

In RECOS therapy, a neuropsychological battery exploring the five cognitive functions suggested for the training is used to assess patients' cognitive impairments (Franck et al., 2013). The results of the neuropsychological tests were converted to a standard score (mean: 10; S.D.: 3).

For the present study, the battery was composed of 11 neuropsychological tests. Three tests concerned executive functions and were selected as the main cognitive outcomes. They were therefore measured in baseline and in post-assessment in both groups of patients.

2.3.1. Color-Word Stroop Test (Godefroy et al., 2010)

When the name of a color (e.g., "blue," "green," or "red") is printed in a color not denoted by the name (e.g., the word "blue" printed in green ink instead of blue ink), naming the color of the word takes longer and is more liable to errors than when the color of the ink matches the name of the color. The Color-Word Stroop Test is used to assess inhibitory processing in selective attention. The interference score has been considered for the evaluation.

2.3.2. Matrix Reasoning Test (Wechsler, 2000)

The Matrix Reasoning Test evaluates the participant's ability to solve non-verbal visual analogies and identify patterns. One block in the matrix is left blank. To solve it, the participant needs to select the correct missing picture from a number of choices to complete the pattern.

2.3.3. Tower of Hanoi Test (TOH – Delis et al., 2001)

The TOH is a complex problem-solving task used for the assessment of planning capacity. It consists of three rods, and a number of disks of different sizes that can slide onto any rod. The goal is to move the disks from one position to another in the fewest possible moves while adhering to specific rules. The total achievement score is considered for the evaluation.

2.4. RECOS therapy

The RECOS therapy aims to improve the participants' skills in one or more cognitive areas in a specific and personalized way. The great heterogeneity of clinical and cognitive manifestations of schizophrenia prompted us to develop specific training modules. The program targets five main cognitive functions (Selective attention, Verbal memory, Visuo-spatial attention and memory, Working memory, and Reasoning), as well as speed of processing, which is also indirectly trained, given that some exercises include time limits. RECOS modules include both computerized exercises with an increased level of difficulty, and paper/pencil exercises. Exercises were designed by the *Scientific Brain Training Company* (Villeurbanne, France) and adapted by Vianin et al. (2007) for use in schizophrenia. Personalized homework allows what was trained during sessions to be transferred to everyday life (Vianin, 2012).

2.5. Inclusion criteria

Assignment to one of the five training modules is determined according to standard scores obtained through the neuropsychological assessment. Regarding the potential difference between what can be observed in testing and functioning in real life situations, we considered the functional outcome of the deficits before choosing the training module(s). Functional outcome was measured by a semi-structured questionnaire called *Echelle d'évaluation des répercussions fonctionnelles* (Functional outcome assessment scale, Vianin, 2013) developed specifically for RECOS. As our main hypothesis concerned increased activation of frontal areas after RECOS therapy, only patients who showed difficulties in executive functioning in their everyday life participated in the present study. Consequently, the RECOS group participated in the module called *Reasoning* dedicated to the training of executive functions.

2.6. MRI protocol

The protocol was approved by the ethical committee of the medical faculty of the Lausanne University. All the participants provided informed written consent after the procedure had been fully explained.

2.6.1. Verbal fluency task

The verbal fluency task was given within an fMRI block design, with an alternation of four activity and four rest blocks. Each of the eight blocks lasted 25 s. Throughout the activity periods, the subjects had to produce silently as many words as possible beginning with the letter (i.e., P, A, T, and M) that was visually presented (one letter per activity period). During the rest condition, patients saw a black screen and were instructed to relax. Each block consisted of five volumes collected in 25 s. Presentation of stimuli was controlled by the E-Prime software package (*Psychology Software Tools*, Pittsburgh, PA, USA). The visual stimuli were projected on a transparent screen in front of the scanner tunnel which could be viewed by the subject through a mirror system mounted at the top of the MRI head coil.

2.6.2. Image acquisition

The MRI protocol was performed on a Siemens 3T Tim Trio scanner and included a sagittal T1-weighted gradient-echo sequence (MPRAGE, 160 contiguous slices, 1 mm isotropic voxel, TR=2300 ms, TE=2.98 ms, and field of view=256 mm) and the fMRI acquisition. Functional scans were acquired with a single-shot echo-planar gradient-echo sequence (EPI, TR=5000 ms, TE=30 ms, flip angle=90°, and field of view=256 mm). The 28 axial slices (matrix size 128 × 128 with 4-mm slice thickness) were aligned with the anterior commissure–posterior commissure line. During the verbal fluency task, five volumes of data were collected in each of the four activity and four rest blocks (40 volumes in all).

2.6.3. Image analysis

Statistical Parametric Mapping-5 (SPM5, Wellcome Department of Imaging Neuroscience, London, England; www.fil.ion.ucl.ac.uk) was used to analyze the data. For each subject, motion correction between volumes was performed by means of rigid body transformations. Images were also corrected for slice-timing differences and then coregistered to the high resolution T1w acquisitions. The anatomical images were normalized using the Montreal Neurological Institute (MNI) T1 template, and the normalization parameters were applied to the functional images, which were finally smoothed with an 8-mm Gaussian kernel. All the mentioned preprocessing steps minimized non-task-related variability, and thus the source of error, within the acquired fMRI time series.

2.7. Statistical analysis

Statistical analyses for single subjects were performed according to the General Linear Model (Friston et al., 1995), and group analyses were performed modeling within-subject variability as fixed effects. Contrasts of interest were thresholded for peak height at $p=0.05$ (family-wise error (FWE) corrected), with an extent threshold (k) of 10 voxels.

The limitation of modeling intra-subject variability as a fixed effect implies that the results described should be considered descriptive, thus providing valid inference only about the specific sample used (Friston et al., 1999).

The experiment included two factors of two levels each: Group (RECOS or TAU) and Time (T1 or T2). The main effects of each factor, as well as interactions between them, have been tested modeling intra-subject variance as fixed effects. Clusters of significance underwent post-hoc comparisons by means of the corresponding *t*-tests. Moreover, to remove baseline differences between the two groups, we first created a mask of brain regions that already showed a difference in activation between RECOS and TAU at T1. Then, we explored the effect of the RECOS program on the verbal fluency task by comparing the brain activity at post-assessment (T2) between the RECOS group and the TAU group excluding regions already present in the mask. This approach allows us to analyze the additional recruitment at post-assessment of brain regions that did not show a statistical difference between the groups at T1. Next, we reported the analysis comparing the RECOS group between T1 and T2.

Finally, as the neuropsychological data suit Gaussian distributions and the variances between groups are homogenous, the key assumptions to compute analyses of variance (ANOVAs) are fulfilled (Field, 2005). Thus, we compared the improvement between the RECOS group and the TAU group by computing 2 (time: baseline and post-assessment, T1 and T2) × 2 (group: RECOS and TAU) ANOVAs on the measures of the executive neuropsychological test performance.

3. Results

3.1. fMRI analyses

Fig. 1 illustrates the network involved when performing the covert fluency task in the whole sample. This wide network, which is comparable to those in previous studies (e.g. Frith et al., 1995), includes the left supplementary motor area, the right cerebellum, the right insula lobe, the right precentral gyrus, the left middle and superior temporal gyrus, and the inferior frontal gyrus bilaterally.

ANOVA results for the Group effect (independent from the session considered) showed several activated clusters with a predominance of the left hemisphere (Fig. S1). The most significant and extended clusters were located in the left inferior frontal gyrus. The inferior parietal lobule, the precentral gyrus, and the middle occipital gyrus showed a bilateral activation with a predominance of the left hemisphere. Activations of the precuneus and the supplementary motor area were mainly symmetrical. The same pattern was found in the interaction between Group and Time (Table S1). This particular configuration of the results requires a careful post-hoc *t*-test analysis to determine the origin of the effect.

Indeed, the comparison between the RECOS group and the TAU at T1 mainly revealed significant differences between the groups in two clusters in the left precentral gyrus (Brodmann area (BA) 44; $x, y, z=-54, 4, 26$ and $-54, 8, 36$ respectively) and in the left post-central gyrus (BA 6; $x, y, z=-54, -16, 52$ respectively). Then, the comparison between the RECOS and the TAU groups at T2 revealed improvements after the RECOS program (between-subject comparisons excluding baseline differences) in brain areas such as the right precentral gyrus, the left inferior frontal gyrus, p. Triangularis (Broca, see Fig. 2) and the left middle cingulate cortex. Likewise, the results of the differences between brain activation at T2 and T1 in the RECOS group revealed an increase of brain activation after the therapy in the right precentral gyrus, the right angular gyrus, the right supramarginal gyrus, and the left supplementary motor area (see Table 2).

3.2. Neuropsychological data analyses

As compared with the control group, results indicate that the RECOS group participants improved their performance in the Color-Word Stroop Test and the Matrix Reasoning Test (see Table 3). We did not, however, find any Time × Group interaction effects for TOH performance.

4. Discussion

The present study provides fMRI evidence of increased activation after therapy in frontal areas and confirms that observed cognitive improvements after remediation are related to changes in specific aspects of brain function (Wykes et al., 2002). Wykes et al. study showed increased activation in regions associated with working memory after cognitive remediation therapy, while our study showed an increased activation in Broca's area during a covert verbal fluency task after RECOS therapy. Interestingly, Bor et al. (2011) suggested that increased activation in Broca's area observed in patients with schizophrenia after cognitive remediation could be explained by the use of language functions by the participants. Consistently, we assume that RECOS therapy enables such frontal activation by encouraging the use of verbal mediation techniques such as current and retrospective verbalization.

Many studies found reduced language lateralization in schizophrenia. Weiss et al. (2004) showed that healthy controls and patients with schizophrenia recruit Broca's area during a verbal fluency task, but that activation is primarily in the left hemisphere in the controls and more bilateral for patients. In our study, increased activation in the RECOS group was observed in the left inferior frontal gyrus and appears to involve more lateralized language activation after cognitive remediation. As Mitchell and Crow (2005) suggest that a failure of lateralization of language functions could explain the social interaction deficits in schizophrenia, it would be interesting to analyze in a further and more controlled study whether RECOS therapy could really induce more lateralized language activation.

Considering recent studies, Penadés et al. (2013) underlined that frontal and prefrontal dysfunction in schizophrenia (Meyer-Lindenberg et al., 2001) need not be equated with the simple notion of hypofunction but may be the consequence of widespread

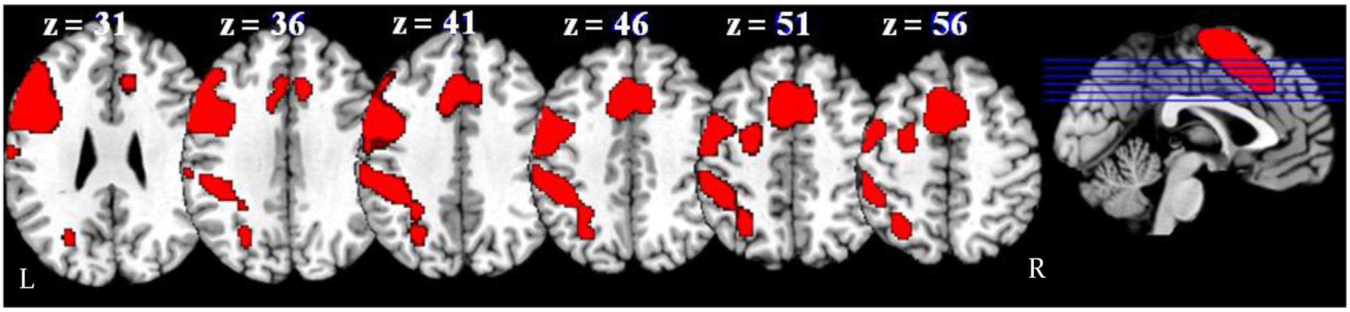

Fig. 1. T1 cerebral activation, significant at $p_{(FWE)} < 0.05$, of the whole sample ($N = 16$) during the verbal fluency task. *Note*: The z coordinates are shown over the sections. R: Right and L: Left.

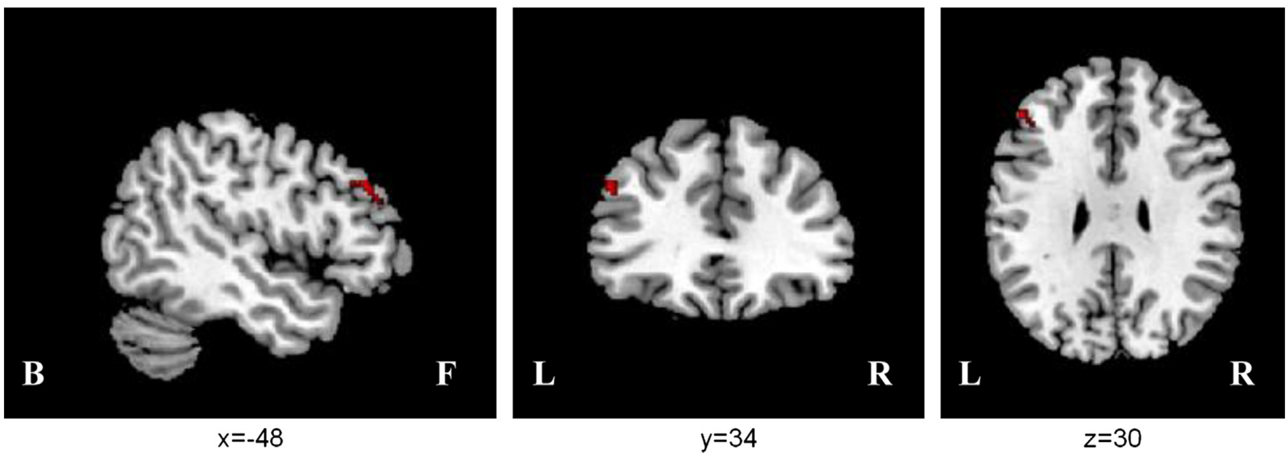

Fig. 2. Broca's area (BA45) activation issued from the comparison between RECOS and TAU at post-assessment (T2). B: Back; F: Front; L: Left; and R: Right.

Table 1
Demographic, clinical and cognitive variables.

	RECOS group ($n=8$)	TAU group ($n=8$)	Statistic[a]	p-Value
Demographic variables				
Age (S.D.)	27.63 (8.2)	30.50 (9.4)	26.00	0.528
Level of education (GREFEX, 2008)[b]	Level 1: $n=2$	Level 1: $n=4$		
	Level 2: $n=6$	Level 2: $n=3$	2.667	0.264
	Level 3: $n=0$	Level 3: $n=1$		
Male/female	6/2	7/1	0.410	0.522
Clinical variables				
Onset of schizophrenia	20(4)	22.38 (4.1)	20.5	0.224
Duration of illness (in months)	92.13 (68.4)	95.75 (72.2)	31.5	0.958
PANSS total score	61.38 (16.3)	70.75 (12.61)	22	0.328
Medication: mean (S.D.) (chlorpromazine equiv./day)[c]	301.19 mg (231,1) ($n=7$)	261.99 mg (255.8) ($n=7$)	23.5	0.898
Cognitive assessment[d]				
RVLT immediate recall	8.13 (2.85)	6.88 (2.75)	24	0.395
RVLT delayed recall	7 (3.16)	5.50 (2.93)	23	0.339
Logical Memory I – recall	9 (2.62)	8.63 (3.81)	30.5	0.874
Logical Memory I – theme	9.63 (1.3)	9.63 (4.07)	30	0.831
Family Scenes I	7.17 (2.93)	6.13 (4.36)	19	0.513
Family Scenes II	7 (2.37)	6.88 (3.68)	22	0.794
Spatial Memory (Corsi Blocks)	8.88 (2.8)	8.13 (2.23)	28	0.668
Code	7.63 (1.6)	6.38 (2.72)	21.5	0.262
Symbols	7 (3.21)	7.38 (2.77)	28.5	0.711
Digit Span	9.25 (2.31)	8.13 (2.85)	24	0.397
D2 (Gz-F)	5 (1.41)	5.88 (3.36)	30.5	0.866

Abbreviations: PANSS, Positive and Negative Syndrome Scale; and RVLT, Rey Auditory Verbal Learning Test.

[a] Results of Mann–Whitney tests or χ^2 test as appropriate. Data are mean (S.D.) except for *Level of education* and *male/female*.

[b] Level 1: school leaving certification; level 2: high school study level; and level 3: high school diploma and higher education.

[c] Detail of medication for the RECOS group: risperidone ($n=2$), aripiprazole ($n=1$), clozapine ($n=2$), olanzapine ($n=1$), and quetiapine ($n=1$); for the TAU group: risperidone ($n=4$), olanzapine ($n=2$), and quetiapine ($n=1$).

[d] Rey Auditory Verbal Learning Test (RVLT) – immediate recall (Rey, 1966); Rey Auditory Verbal Learning Test (RVLT) – delayed recall (Rey, 1966); Logical Memory I: recall (Wechsler, 2001); Logical Memory I: theme (Wechsler, 2001); Family Scenes I (Wechsler, 2001); Family Scenes II (Wechsler, 2001); Spatial Memory (Corsi Blocks) (Wechsler, 2001); Processing Speed Index (PSI) (Wechsler, 2000); Digit Span (Wechsler, 2000); and D2 (Brickenkamp, 1962).

Table 2
Summary of cerebral activation: post-hoc analyses.

	Brodmann area (BA)	Side	Number of voxels	Stereotaxic coordinates (MNI space)			*t*-Value
				x	*y*	*z*	
RECOS > TAU at T2[a]							
Inferior parietal lobule		Right	162	50	−56	44	7.13
Precentral gyrus	44	Right	69	52	8	42	6.88
Inferior frontal gyrus (p. Triangularis)	45	Left	29	−48	34	30	7.09
Middle occipital gyrus		Left	15	−32	−96	2	5.99
Middle cingulate cortex		Left	12	−2	−36	50	5.62
Superior parietal lobule		Left	10	−20	−74	54	5.27
T2 > T1 in RECOS[b]							
Precentral gyrus	44	Right	54	52	6	42	6.54
Inferior parietal lobule		Left	49	−30	−62	56	6.51
Angular gyrus		Right	48	38	−64	58	6.47
Inferior occipital gyrus		Right	28	36	−88	−8	5.83
Middle occipital gyrus		Left	25	−32	−94	0	6.20
Supramarginal gyrus		Right	16	60	−28	40	5.58
SMA	6	Left	13	−6	2	74	6.78
Paracentral lobule	6	Left	12	−6	−20	76	6.81

[a] Comparison between RECOS and TAU at post-assessment (T2) excluding brain regions showing a difference in activation between RECOS and TAU at T1.
[b] Subtraction of preassessment (T1) from post-assessment (T2) within the RECOS group. SMA, supplementary motor area. MNI, Montreal Neurological Institute.

Table 3
Neuropsychological data for all participants at T1 and T2 and results of the analyses of variance.

	T1		T2		Main effect of time	Main effect of group	Interaction time × group
	RECOS	TAU	RECOS	TAU			
Stroop	8.25 (4.50)[a]	7.00 (3.74)	10.25 (4.23)	7.50 (3.15)	$F(1, 12)=2.76$; $p=0.122$	$F(1, 12)=0.50$; $p=0.495$	$F(1, 12)=7.68$; $p=0.017$
Matrix Reasoning	8.38 (2.83)	7.63 (2.97)	11.25 (3.85)	7.83 (2.23)	$F(1, 12)=4.15$; $p=0.064$	$F(1, 12)=0.93$; $p=0.354$	$F(1, 12)=17.71$; $p=0.001$
Tower of Hanoi	8.69 (3.81)	8.06 (3.70)	10.13 (4.40)	9.42 (4.90)	$F(1, 12)=3.55$; $p=0.084$	$F(1, 12)=0.20$; $p=0.666$	$F(1, 12)=0.07$; $p=0.792$

[a] Mean (S.D.).

alterations of the connectivity between various brain networks. For this purpose, the study of Penadés et al. explored the impact of the cognitive remediation therapy on structural connectivity, integrating structural MRI and fMRI techniques. Their results showed that brain network activation patterns changed after cognitive training. Interestingly, cognitive improvement, functional changes, and structural changes were significantly associated in that study. Increased activation observed in our study may therefore reflect increased functional connectivity between areas associated with language production rather than normalization of Broca′s area activation after cognitive training. Further studies are needed to explore structural and functional changes after cognitive training, as data are still missing to show that structural deficits can produce functional deficits at distant cerebral regions.

Neuropsychological analyses showed better performance in tasks requiring executive abilities (more specifically in the Color-Word Stroop Test and in the Matrix Reasoning Test) after RECOS therapy. Thus, we might hypothesize that increased fronto-cortical activations were associated with improved executive functioning and therefore confirm that cognitive remediation therapy concomitantly changes cognition and brain activation (Bor et al., 2011). Similar behavioral results were observed in our preliminary study, where the TOH was the only executive test in which performance did not improve after cognitive remediation (for details, see Deppen et al., 2011). The large inter-individual differences usually observed in TOH performance probably make it difficult to find significant results in a small number of subjects.

Moreover, we recently showed that RECOS therapy improves performance in the Behavioral Assessment of the Dysexecutive Syndrome (BADS – Wilson et al., 1996), an ecologically valid and reliable assessment (Franck et al., 2013). That finding possibly reflects the translation of cognitive improvements into everyday functioning. Indeed, RECOS therapy is designed to improve deficits in specific skills while promoting the transfer and generalization of skills learned in therapy to everyday life. It develops the ability to change personal thought processes since each participant is requested to analyze performance against strategies he/she has himself/herself developed (Vianin, 2012).

The present study is exploratory in nature and the results have to be interpreted with caution. First of all, only a few studies used fMRI to evaluate the effect of cognitive remediation in patients with schizophrenia. The underlying mechanisms for improvement following cognitive remediation therapy are therefore not well understood. We showed an increased activation in Broca′s area after RECOS therapy. Verbal mediation techniques used during remediation may be involved in these brain changes, but the interpretation of the observed effects remains speculative. Secondly, the sample size is limited, so randomizing such a small number of subjects is methodologically questionable. Thirdly, the possible contribution of antipsychotic medication to the cognitive improvement observed remains to be explored. We were very attentive in the selection of subjects stabilized before their enrollment in the study. However, the dose of medication was not taken into account as a moderating variable. Fourthly, the number of female patients is very low. As healthy women generally produce more words than men and activate different areas during verbal fluency tasks (Halari et al., 2006), it is difficult to generalize the results of the present study to female patients with schizophrenia. Finally, a healthy control group was not included in the study. It is therefore not possible to conclude that the brain-activation patterns were "normalized" after RECOS therapy.

In conclusion, this exploratory study showed that RECOS therapy is associated with changes in fronto-cortical activation, particularly in

Broca's area. Our study confirms that hypofrontality may be improved by cognitive remediation therapy, as shown previously (Wykes et al., 2002; Bor et al., 2011). By asking participants to verbalize their own strategies during and after the training exercises, RECOS therapy allows the participants to become aware of their own problem-solving strategies and to generate new ones if they did not succeed in the task. We assume that these verbalization techniques are the main factor underlying the brain changes observed in the present study.

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Appendix. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2014.01.004.

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