Psychiatry Research: Neuroimaging 221 (2014) 204–209

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

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

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ARTICLE INFO

Article history:
Received 21 February 2013
Received in revised form
21 December 2013
Accepted 10 January 2014
Available online 18 January 2014

Keywords:
Functional magnetic resonance imaging
Executive function
Frontal area
Verbalization
Verbal fluency

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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http://dx.doi.org/10.1016/j.pscychresns.2014.01.004

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