Cognitive Remediation Therapy in Adolescents With Early-Onset Schizophrenia: A Randomized Controlled Trial

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Objective: Cognitive impairment is an enduring and functionally relevant feature of early-onset schizophrenia (EOS). Cognitive remediation therapy (CRT) improves cognition and functional outcome in adults with schizophrenia, although data in adolescents with EOS remain scarce. The purpose of this study is to examine the efficacy of CRT in improving cognition and functional outcomes in a sample of symptomatically stable but cognitively disabled adolescents with EOS. **Method:** We performed a randomized, controlled trial of individually delivered CRT plus treatment-as-usual compared with treatment-as-usual (TAU). Fifty adolescents with EOS were randomly assigned to receive CRT (n = 25) or TAU (n = 25) and were included in an intention-to-treat analysis. Clinical symptoms and cognitive and functional performance were assessed before and after treatment in both groups and after 3 months in the CRT group. Cognitive domains were defined according to the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) consensus battery and averaged in a global cognitive composite score. **Results:** After CRT, significant improvements were found in verbal memory and executive functions, with medium-to-large effect sizes (ES). The derived cognitive composite score showed an improvement after the treatment, with a large ES. This change was reliable in more than two-thirds of the treated patients. Medium-sized ES were found for improvements after CRT in daily living and adaptive functioning, whereas large ES were observed for improvements in family burden. With the exception of functional gains, these changes were maintained after 3 months. **Conclusion:** CRT appears to be a useful intervention strategy for adolescents with EOS. Cognitive improvements can be achieved through CRT, although further research is warranted to determine the durability of functional gains. Clinical trial registration information—Cognitive Remediation Therapy (CRT) in Adolescents With EOS; www.clinicaltrials.gov; NCT01701609. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(8):859–868. **Key Words:** early-onset, cognitive remediation therapy, CRT, cognition, functional outcome

Early-onset schizophrenia (EOS) is a severe and debilitating form of schizophrenia that has poor prognosis and functional outcomes[1,2] and that places heavy demands on caregivers.[3] Enduring cognitive deficits are a core feature of the illness that predict chronicity and contribute to poor functional outcomes.[1,4] Because pharmacological interventions have a limited effect on cognitive impairment in EOS,[5] there is a critical need for effective treatments for cognitive deficits in young persons with this condition.[5,6] Cognitive remediation therapy (CRT) uses scientific principles of learning to target cognitive deficits with the ultimate goal of improving functional outcome. There is now a substantial body of evidence in support of its efficacy in adults with schizophrenia.[7]

As most studies of CRT have involved adults with this disorder,[7] data supporting its potential usefulness in adolescents with EOS remain scarce.[3] Wykes *et al.*[8] found that CRT produced clinically significant and lasting improvements in cognitive flexibility in 40 participants, mostly adolescents but also young adults. Although CRT did

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not have a significant direct effect on functional measures, the authors did observe a moderating effect of therapy on symptoms and a positive effect of cognitive change on social functioning. Only 2 studies have been conducted in samples exclusively comprising adolescents. Ueland *et al.*[9,10] found a few short-lived cognitive changes after CRT. This was a study of 26 inpatients either with diagnoses within the schizophrenia spectrum or with other psychotic disorders. In a study of 32 adolescents, Holzer *et al.*[11] found improvements in visuospatial abilities after CRT, as well as enhanced reasoning and inhibition abilities at 6-month follow-up.[12] However, the sample included patients with a high risk of psychosis rather than psychotic illness. As even small cognitive improvements could be of benefit in this group of patients,[8] more research is clearly needed.

The aim of the present study was to examine the efficacy of individual CRT in improving cognition and functional outcomes in adolescents with EOS who were clinically and pharmacologically stabilized. The primary outcomes were changes in measures of different cognitive domains and in the cognitive composite score. Secondary outcomes were functional measures, including those related to daily-living skills, general adaptive functioning, and self-esteem. We also included a measure of perceived burden among the patients' relatives as a result of their role as caregivers. We expected that, in comparison with treatment as usual, CRT would improve both primary and secondary outcomes.

METHOD

Study Participants

Participants were adolescents with EOS recruited from the Department of Child and Adolescent Psychiatry and Psychology of the Hospital Clínic in Barcelona who were referred by their treating psychiatrist. The inclusion criteria were as follows: age between 12 and 18 years; a *DSM-IV-TR* schizophrenia or schizoaffective disorder with onset at age 17 years or earlier; being clinically and pharmacologically stabilized, without changes in antipsychotic treatment during the 6 weeks prior to the baseline assessment; and presence of cognitive impairment. To define cognitive impairment, we adapted the criteria of Penadés *et al.*,[13] taking into account the developmental stage. At least 1 of the following conditions had to be present: 2 discrepant scores (discrepancy is determined when a T-score is more than 1 SD below the level of the patient's IQ), or a normative T-score of less than 37 on the perseverative errors score of the Wisconsin Card Sorting Test (WCST).[14] Diagnoses and stability of psychopathology were verified by 1 of the child and adolescent psychiatrists of the research team using *DSM-IV-TR* criteria and based on clinical interviews with patients and their families. Exclusion criteria were as follows: current IQ yielding a T-score of less than 30 (equivalent to an IQ of 70); active substance use disorder; organic brain syndrome or neurological disorder; and having received electroconvulsive therapy in the previous 6 months.

Dropouts and Final Sample

A total of 51 patients were randomized to the groups. Of these, 21 dropped out before the posttreatment assessment was carried out (Figure 1). Patients who dropped out were more likely to have had a diagnosis of schizoaffective disorder ($\chi^2 = 4.78$, $p = .029$), and they had a higher IQ ($t = 3.16$, $p = 0.003$) than those who completed the posttreatment assessment. The dropout rate for patients with a schizoaffective disorder ($\chi^2 = 2.01$, $p = .311$) and with higher IQ ($t = 2.04$, $p = .055$) was similar for both the CRT and TAU groups. No other significant differences were found on core clinical, demographic, functional, and cognitive variables. The final sample used for analysis included all but 1 of the randomized participants. One participant was excluded because of a change in diagnosis to bipolar disorder with psychotic features during the intervention phase of the study.

Study Design

This was a randomized, single-blind, parallel-group, controlled study of CRT plus treatment as usual compared with a treatment-as-usual (TAU) group (www.clinicaltrials.gov: NCT01701609). Restricted randomization was conducted using permuted blocks with a fixed size of 8 patients being allocated in a 4:4 ratio to receive CRT or TAU according to a computerized allocation sequence. Although the instructor who administered the CRT (as well as patients and their relatives) were aware of the allocated intervention, the psychiatrists and neuropsychologists who assessed outcomes were blinded to group allocation and unaware of the results from the other source of data. Relatives were also unaware of the neurocognitive data when providing the relevant information.

The assessments before and after treatment were the main focus of the study. In addition, patients in the CRT group were reassessed after 3 months. For clinical reasons, patients in the TAU group underwent CRT immediately after completing the trial and were not assessed after 3 months.

Written informed consent was obtained from the parents of all patients after a full description of the study, and the adolescents' assent was also obtained. The patients were compensated through their parents for the time and travel costs related to their participation in the study. The study was approved by the ethics committee of the Hospital Clínic of Barcelona.