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Predictors of cognitive and functional improvement and normalization after cognitive remediation in patients with schizophrenia

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ABSTRACT

Objective: Although the efficacy of cognitive remediation interventions has been demonstrated in several experimental studies on schizophrenia, few studies have investigated the predictors of response to such interventions. We were interested in determining what factors contribute to a positive outcome after cognitive rehabilitation and whether different factors are associated with different degrees of improvement in cognitive and real-world functioning in individual patients after cognitive remediation.
Methods: The study sample consisted of 56 patients with schizophrenia who had completed a 6-month cognitive remediation intervention and showed different cognitive and functional outcomes. Measures of cognitive and functional amelioration after cognitive remediation were analyzed in relation to patients' clinical, neuropsychological and functional variables at baseline using logistic regression analysis.
Results: Lower antipsychotic intake at baseline predicted cognitive improvement, whereas lower antipsychotic intake, severity of specific symptoms, and higher neurocognitive functioning (particularly executive functions and verbal memory) at baseline were associated with cognitive normalization after remediation treatment. Functional improvement was predicted by lower patient age and type of cognitive remediation intervention, whereas functional normalization was related to lower baseline antipsychotic intake and, at a trend level, to higher executive functioning and type of cognitive remediation intervention.
Conclusion: Cognitive remediation could be more effective in younger, less disorganized, and cognitively less impaired patients, who take a smaller amount of antipsychotics. The predictive role of lower antipsychotic dosage on cognitive and functional outcome after remediation suggests either that patients with less severe illness could gain better advantage from cognitive remediation interventions or that high dose or complex antipsychotic therapy may limit the effectiveness of such interventions.

1. Introduction

Cognitive dysfunctions are a core feature of schizophrenia (Green et al., 2004; Keefe et al., 2006) and have been shown to play a major role in the functional outcome of the disorder (Bowie et al., 2006, 2008). Various cognitive remediation interventions for schizophrenia have been developed in recent years and adopted in the multimodal treatment approaches to schizophrenia. The efficacy of such interventions in ameliorating cognitive performance and psychosocial functioning is now well recognized (McGurk et al., 2007; Grynszpan et al., 2010; Wykes et al., 2011; Medalia and Saperstein, 2013). Despite the amount of data supporting the benefits of cognitive remediation interventions in schizophrenia, a number of questions remain to be answered. Identification of potential predictors of effectiveness of cognitive rehabilitation is of primary interest to researchers and clinicians, because the efficacy of treatments largely depends on the appropriate selection of individuals and treatment methodologies (Medalia and Richardson, 2005; Bowie et al., 2013; Kontis et al., 2013; Medalia and Saperstein, 2013). Few studies have investigated the relationship between baseline characteristics and the response to cognitive remediation interventions in patients with schizophrenia. A study by Medalia and Richardson (2005) found that baseline cognitive performance, intrinsic motivation and greater clinician experience predicted improvement in cognitive performance in patients with schizophrenia who participated in the Neuropsychological Educational Approach to Remediation (NEAR) program. Another study by Fiszdon et al. (2005) showed that better vigilance, better immediate verbal memory and less hostility predicted remediation success and accounted for 70% of the chance of amelioration in a selected memory task (Wechsler Adult Intelligence Scale

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[WAIS] digit span) after Neurocognitive Enhancement Therapy (NET). Eack et al. (2011) showed that greater neurobiological reserve (pretreatment cortical surface area and gray matter volume) predicted a rapid social-cognitive response to cognitive enhancement therapy (CET) in the first year of treatment. Kontis et al. (2013) showed that younger, but not older patients with schizophrenia, improved in working memory performance after cognitive remediation. This result is complemented by the one of Bowie et al. (2013) that evidenced that early course patients had lager improvements in cognitive measures such as processing speed and executive functions than patients in the chronic course of schizophrenia. Research on the potential predictors of psychosocial improvement after remediation interventions is sparse. Kurtz et al. (2009) demonstrated that after 1 year of Computer-Assisted Cognitive Remediation (CACR), a measure of everyday life skills, assessed with the University of California Performance-based Skills Assessment (UPSA), was predicted by baseline verbal learning performance. Moreover, in a controlled study by Bosia et al. (2007), it was demonstrated that catechol-*O*-methyltransferase polymorphism may affect individual capacity to recover from cognitive deficits after 3 months of CACR intervention, with a significantly greater improvement in the Quality of Life Scale total score in Met carriers on active treatment compared with Val/Val carriers on placebo. More recently, Bowie et al. (2013) demonstrated larger improvement in adaptative competence and real-world work skills in patients with early- vs long-term course schizophrenic illness.

In a previous prospective controlled study performed by our group, we demonstrated the effectiveness of different modalities of cognitive remediation in schizophrenia, i.e. the cognitive subprograms of the Integrated Psychological Therapy (IPT-cog), and CACR (Cogpack), compared with usual rehabilitative interventions in a group of patients with schizophrenia treated in a naturalistic setting of care (Vita et al., 2011a).

In this study, we examined whether specific factors differentiated those individuals who showed a positive response to cognitive remediation and those who did not in cognitive and psychosocial functioning domains to possibly identify the characteristics that predict outcome in individual patients. We were also interested in analyzing whether different factors were associated with different degrees of amelioration in both cognitive and real-world functioning in individual patients after cognitive remediation.

2. Materials and methods

2.1. Participants

Participants were patients who had taken part in a previous study performed by our group (Vita et al., 2011a) in which 84 patients fulfilling the diagnostic criteria for schizophrenia according to the DSM-IV-TR (American Psychiatric Association, 2000), have been followed up naturalistically in three rehabilitative centers at the department of Mental Health of the Spedali Civili Hospital in Brescia (Italy) and Cremona Hospital, for a period of 6 months. Exclusion criteria were: (a) a concomitant diagnosis of mental retardation (as revealed by a Wechsler Adult Intelligence Scale—Revised (WAIS-R) (Wechsler, 1981) full scale IQ less than 70) or substance use disorder; (b) severe positive symptoms or impulsive behavior requiring a higher security setting; (c) significant changes in psychopathologic status (requiring hospitalization or major change in pharmacologic treatment) in the last 3 months; (d) age less than 18 or more than 50 years. These are the same criteria for exclusion of patients to the rehabilitative centers where the study was conducted, according to the admission/discharge criteria for day centers and rehabilitation centers in the Lombardia Region, Italy, so that no further selection of patients among those treated in these centers was done.

Fifty-six patients received a cognitive remediation intervention in addition to usual rehabilitation intervention. In particular, twenty-six patients received the first 2 subprograms (cognitive differentiation and social perception) of the Integrated Psychological Treatment (IPT-cog), and 30 patients received a CACR intervention (for details see Vita et al., 2011a). The IPT is a group-based structured cognitive behavioral program for schizophrenia in which neurocognitive remediation and social cognitive remediation are integrated with psychosocial rehabilitation (Brenner et al., 1994). The IPT-cog groups, composed of 8–10 patients, attended therapy sessions twice a week, 45 min each session, for 24 weeks. They were conducted by one trained psychiatrist or psychologist and another professional who administered the 2 cognitive subprograms following the IPT manual (Brenner et al., 1997). The CACR used the Cogpack (Marker Software®) program. The Cogpack includes different neurocognitive exercises that can be divided into domain-specific exercises, aimed at training specific cognitive areas among those known to be impaired in schizophrenia (verbal memory, verbal fluency, psychomotor speed and coordination, executive function, working memory, attention) and non-domain-specific exercises that require the use of various functions at the same time and engage culture, language and calculation skills. The CACR was administered individually twice a week, in 45-min sessions, for 24 weeks. Another group of patients ($N = 28$) had been followed up with the usual rehabilitation interventions and, for the same period of time, received non-cognitive specific rehabilitation interventions (such as expressive groups as art therapies, physical training, or occupational therapies), with the same frequency and duration of cognitive remediation interventions (Rehabilitation (REHAB) program). In addition to participating in the IPT-cog, CACR or REHAB programs, the patients continued with standard psychiatric care provided by a multidisciplinary mental health team, including other non-cognitive-oriented rehabilitative interventions aimed at improving patients' skills, social relationships or work abilities, individually tailored in relation to clinical needs and personal preferences and delivered in a balanced way between groups (Vita et al., 2011a).

All patients received an antipsychotic treatment at baseline and were then maintained on pharmacologic treatment during the study period but the drug dose or regimen could be modified as needed. In particular, 15 patients received a first generation antipsychotic therapy, either as a monotherapy or as an add-on to a second generation therapy, and 41 patients were treated with second generation antipsychotics. Use of benzodiazepines and anticholinergics was allowed, based on treating psychiatrist's clinical judgment. Doses of antipsychotics taken were calculated as chlorpromazine equivalents (CPZ-eq) using the conversion proposed by Woods (2003) both at baseline and throughout the treatment period. Patients were assessed at baseline and after a six-month follow-up with clinical, functional, and neurocognitive measures. In this study, we considered the 56 patients who received a cognitive remediation intervention (IPT-cog or CACR). Demographic data for this group are shown in Table 1.

2.2. Assessment

The participants were clinically assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and the Clinical Global Impression-Severity (CGI-S) scale (Guy, 1976) at baseline and, at the end point of the study, by the psychiatrists who followed up each patient in the psychiatric outpatient units and who were not directly

Table 1
Demographic characteristics of the study sample at baseline.

Variable	Sample at baseline
Number	56
Sex (M:F)	40:16
Age (years)	37.00 ± 10.30
Age at onset (years)	22.43 ± 5.72
Duration of illness (years)	14.87 ± 9.68
Education (years)	10.45 ± 2.91
WAIS-R full scale IQ	86.30 ± 12.71
Dose of antipsychotics at baseline (CPZ-eq)	634.48 ± 387.44